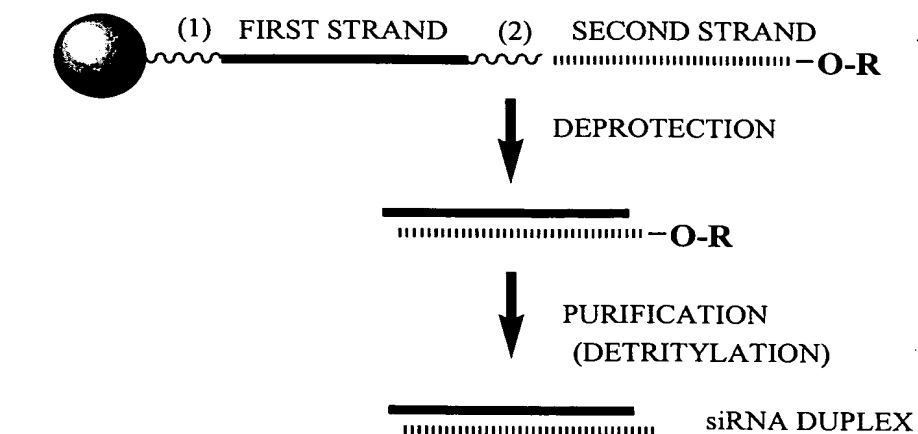


Figure 1

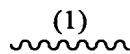


= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP

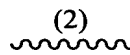
FOR EXAMPLE:

DIMETHOXYTRITYL (DMT)



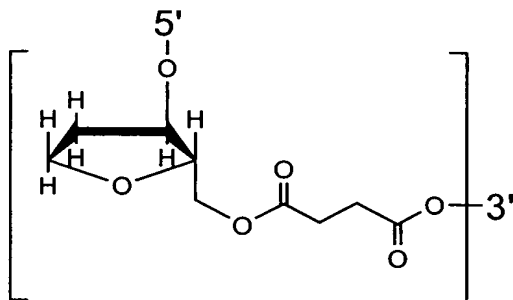
= CLEAVABLE LINKER

(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR
 INVERTED DEOXYABASIC SUCCINATE)

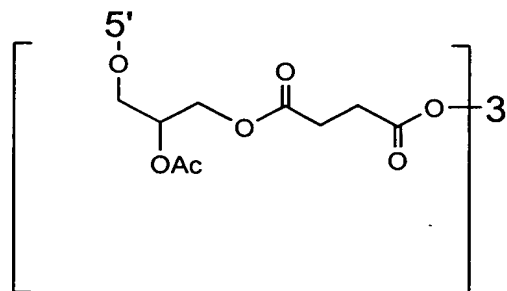


= CLEAVABLE LINKER

(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR
 INVERTED DEOXYABASIC SUCCINATE)



INVERTED DEOXYABASIC SUCCINATE
 LINKAGE



GLYCERYL SUCCINATE LINKAGE

Figure 2

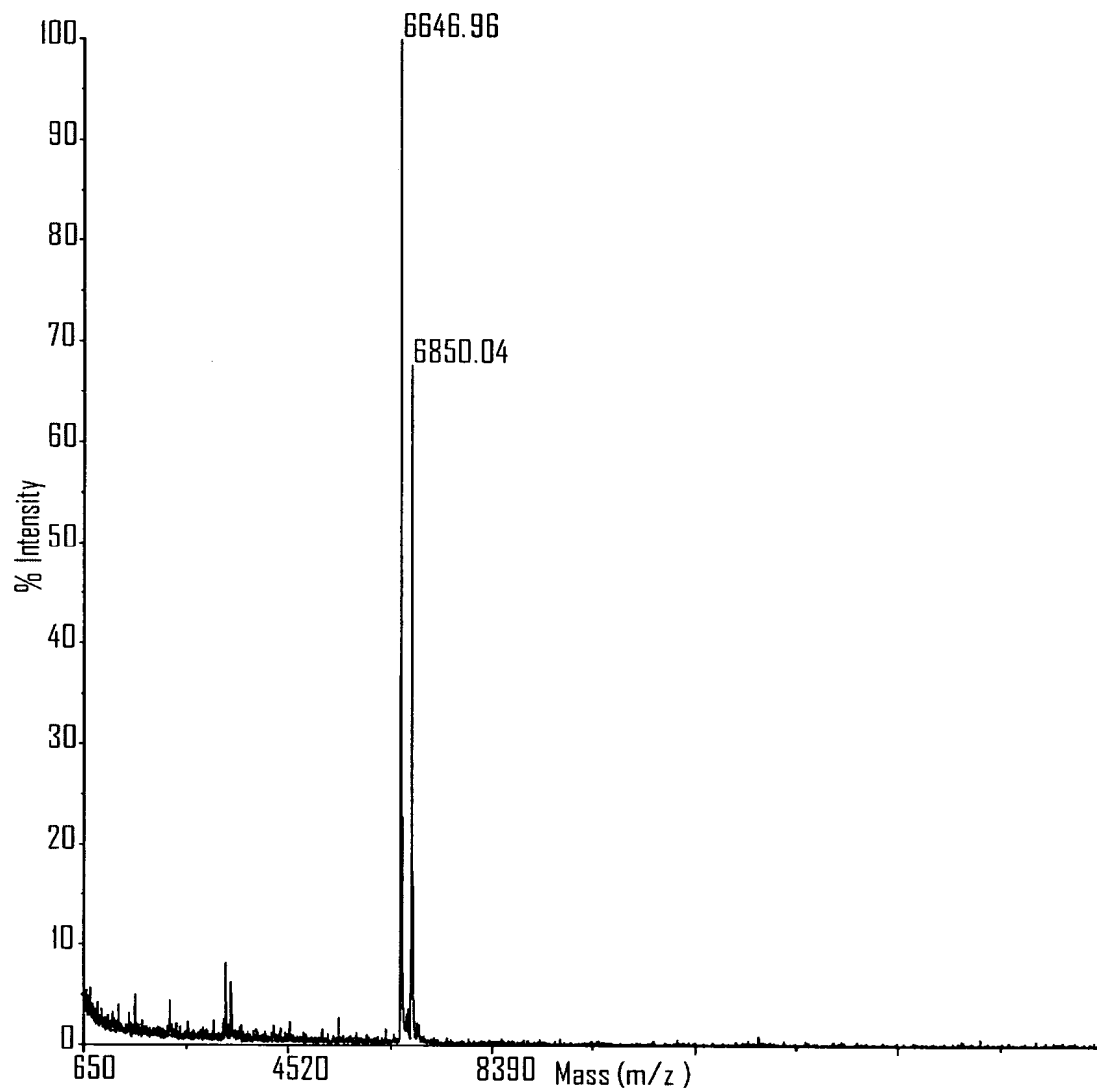


Figure 3

5'-CGUACGCGGAUACUUCGATT (SEQ ID NO: 394) 3'-TTGCAUGCGCCUUAUGAAGCU (SEQ ID NO: 395)	$T_{1/2} = 15 \text{ seconds (control)}$
5'-B cAAccAcAAAUAcAAcAATT B (SEQ ID NO: 396) 3'-TXGuuGGuGuuuuAuGuuGuu (SEQ ID NO: 397)	$T_{1/2} = 138 \text{ min}$
5'-B cAAccAcAAAAuAcAAcAATT B (SEQ ID NO: 396) 3'-TDGuuGGuGuuuuAuGuuGuu (SEQ ID NO: 398)	$T_{1/2} = 3.7 \text{ days}$
5'-B cAAccAcAAAAuAcAAcAATT B (SEQ ID NO: 396) 3'-XTGuuGGuGuuuuAuGuuGuu (SEQ ID NO: 399)	$T_{1/2} = 72 \text{ minutes}$
5'-B cAAccAcAAAAuAcAAcAATT B (SEQ ID NO: 396) 3'-LTGuuGGuGuuuuAuGuuGuu (SEQ ID NO: 400)	$T_{1/2} = 40 \text{ days}$
5'-B cAAccAcAAAAuAcAAcAATT B (SEQ ID NO: 396) 3'-tTGuuGGuGuuuuAuGuuGuu (SEQ ID NO: 401)	$T_{1/2} = 32 \text{ days}$

G, A, U, C = Guanosine, Adenosine, Uridine, Cytidine
 T = Thymidine
 Lower Case = 2'-deoxy-2'-fluoro
 S = phosphorothioate
 B = inverted deoxyabasic
 D = inverted Thymidine
 X = 3'-deoxy Thymidine
 t = L-thymidine
 L = Glyceryl moiety

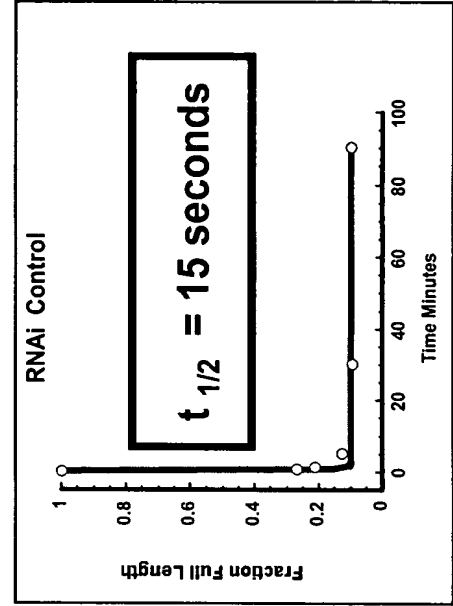


Figure 4

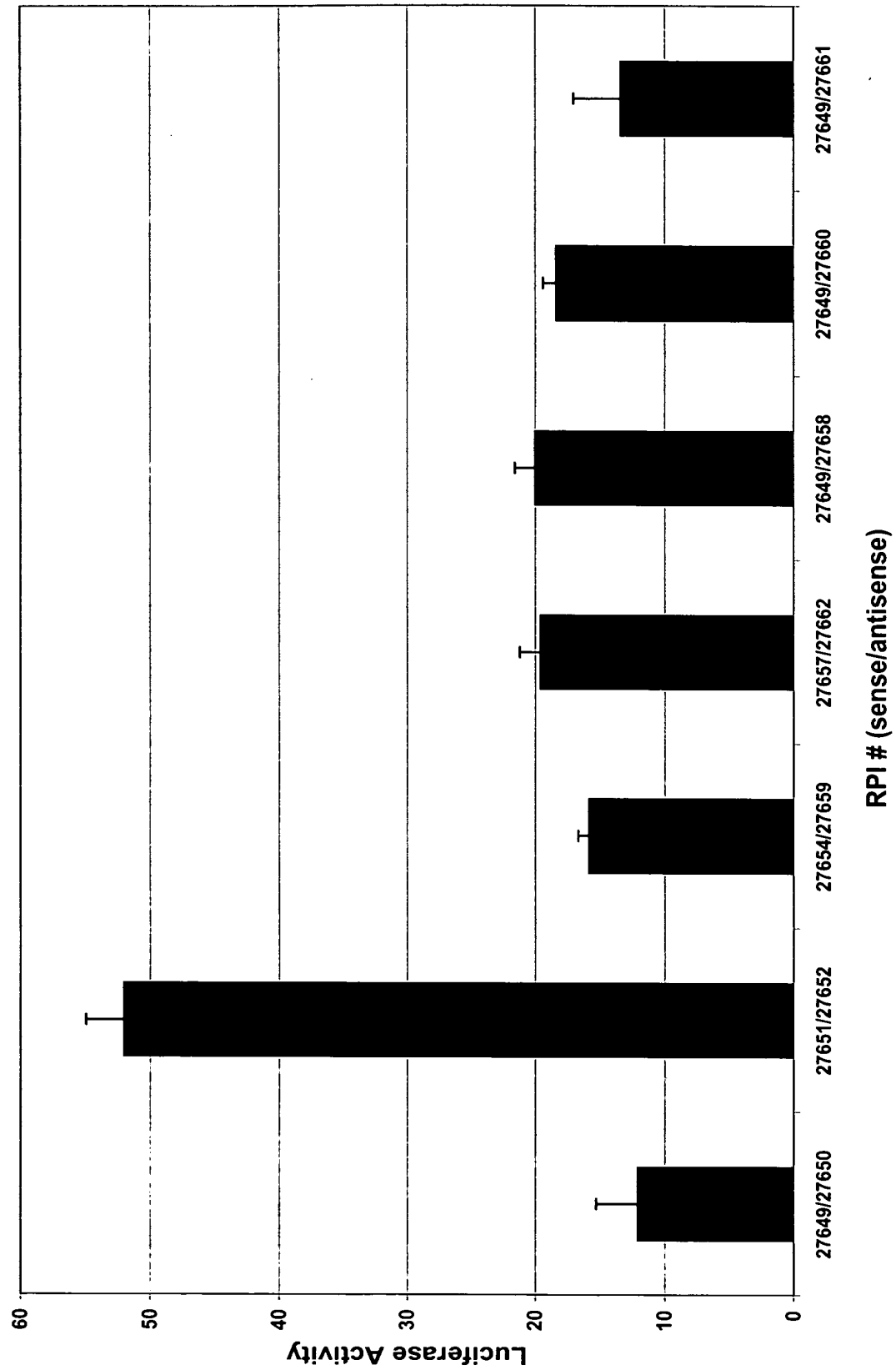


Figure 5

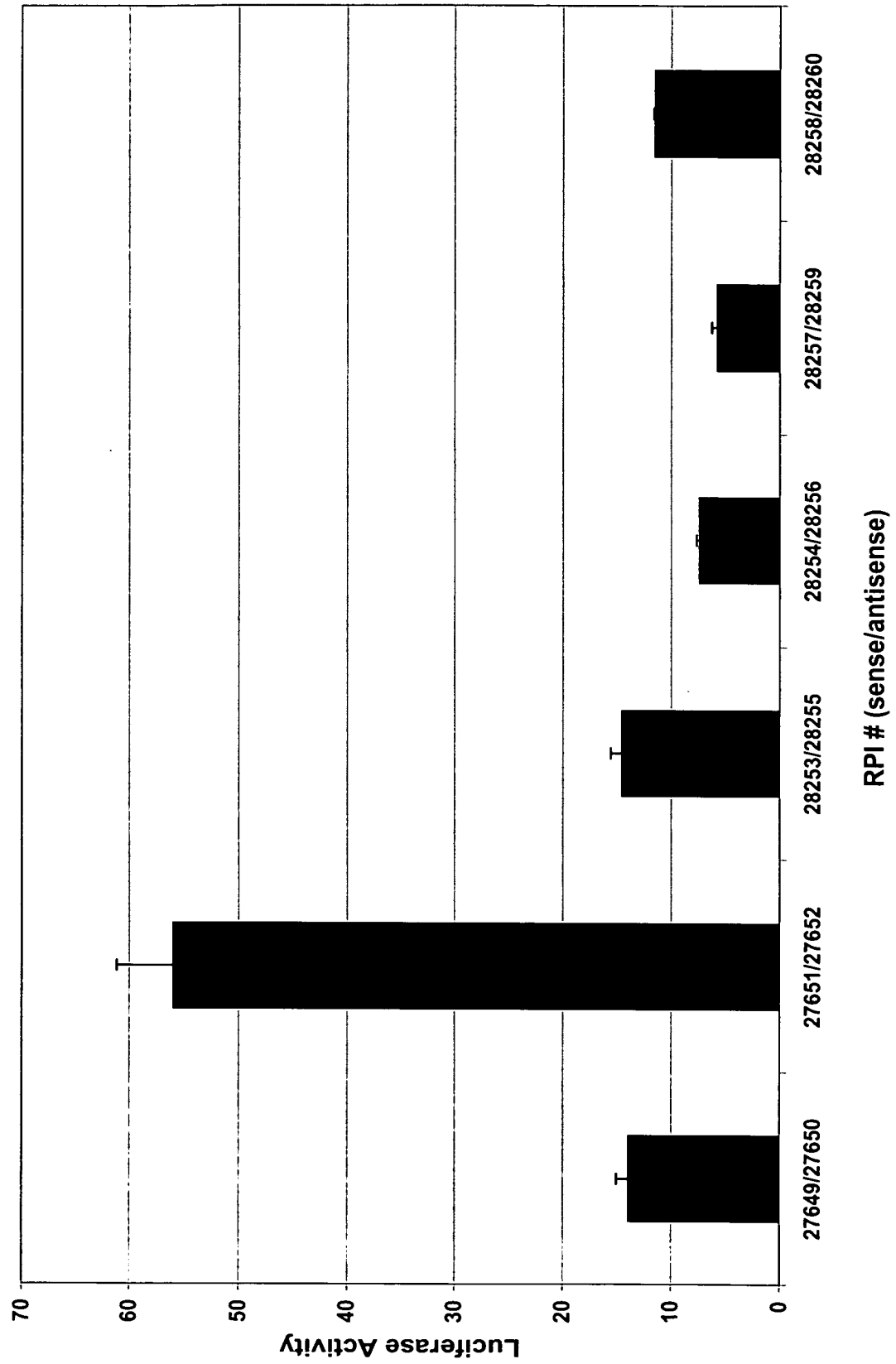


Figure 6

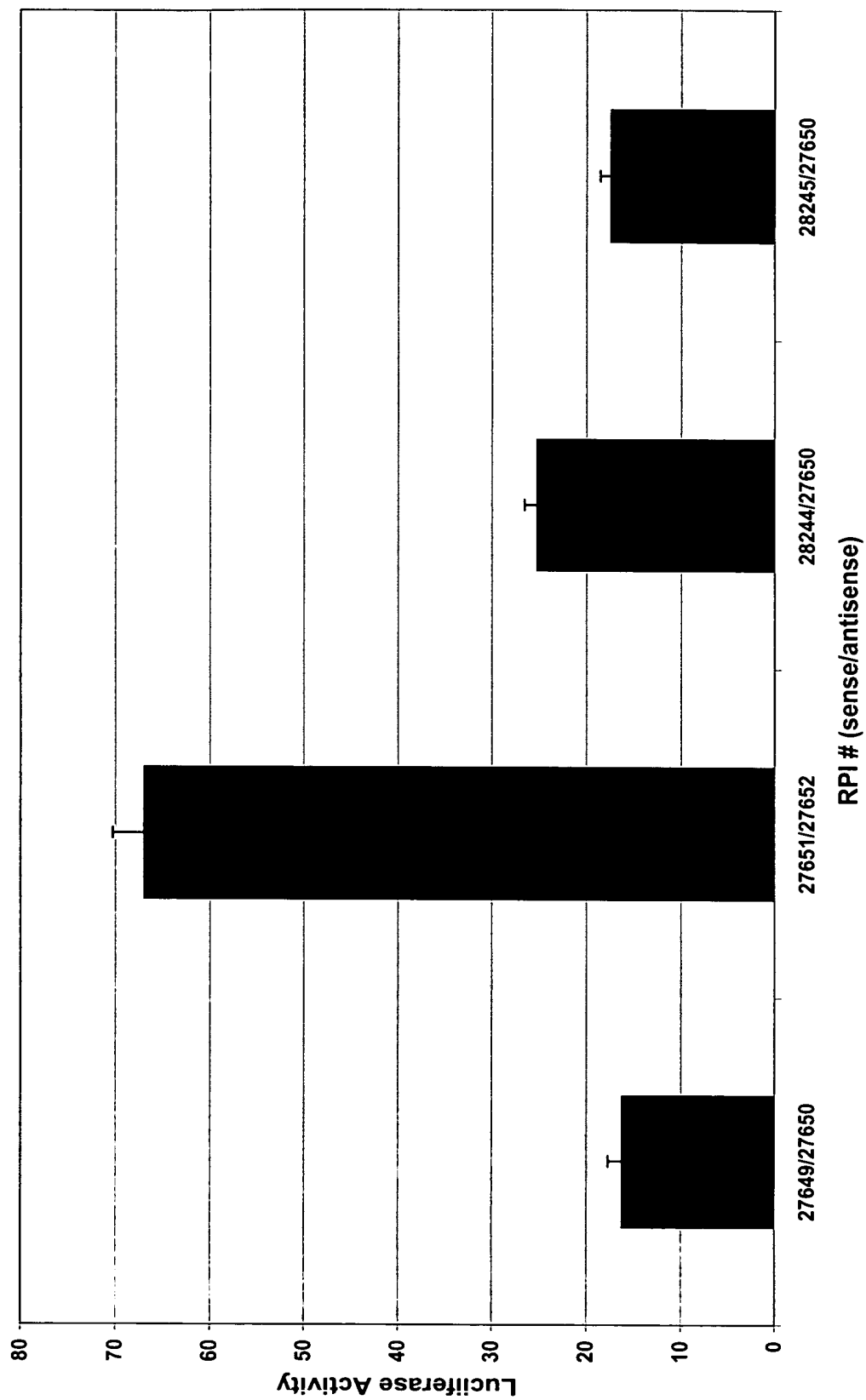


Figure 7

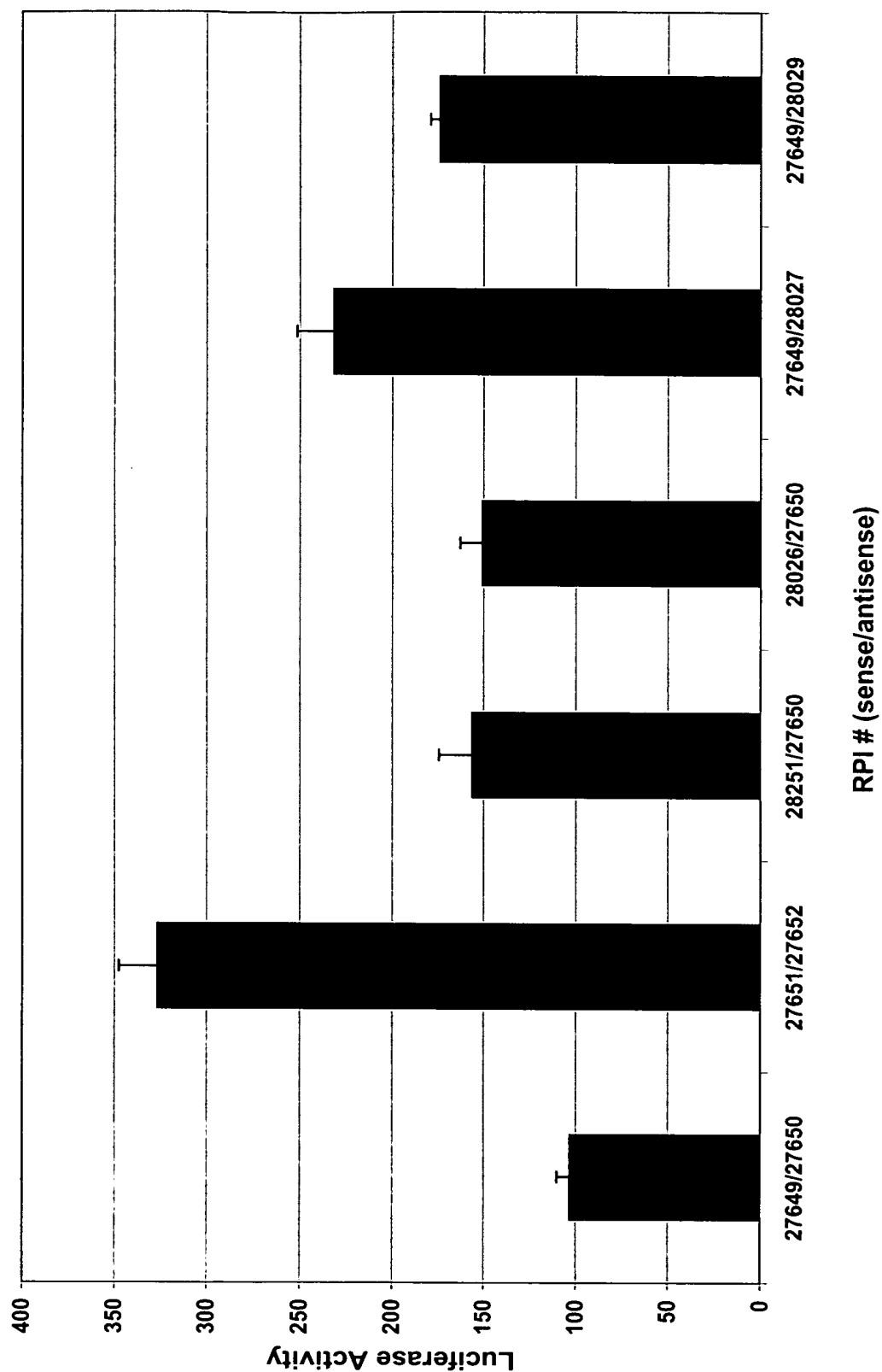


Figure 8

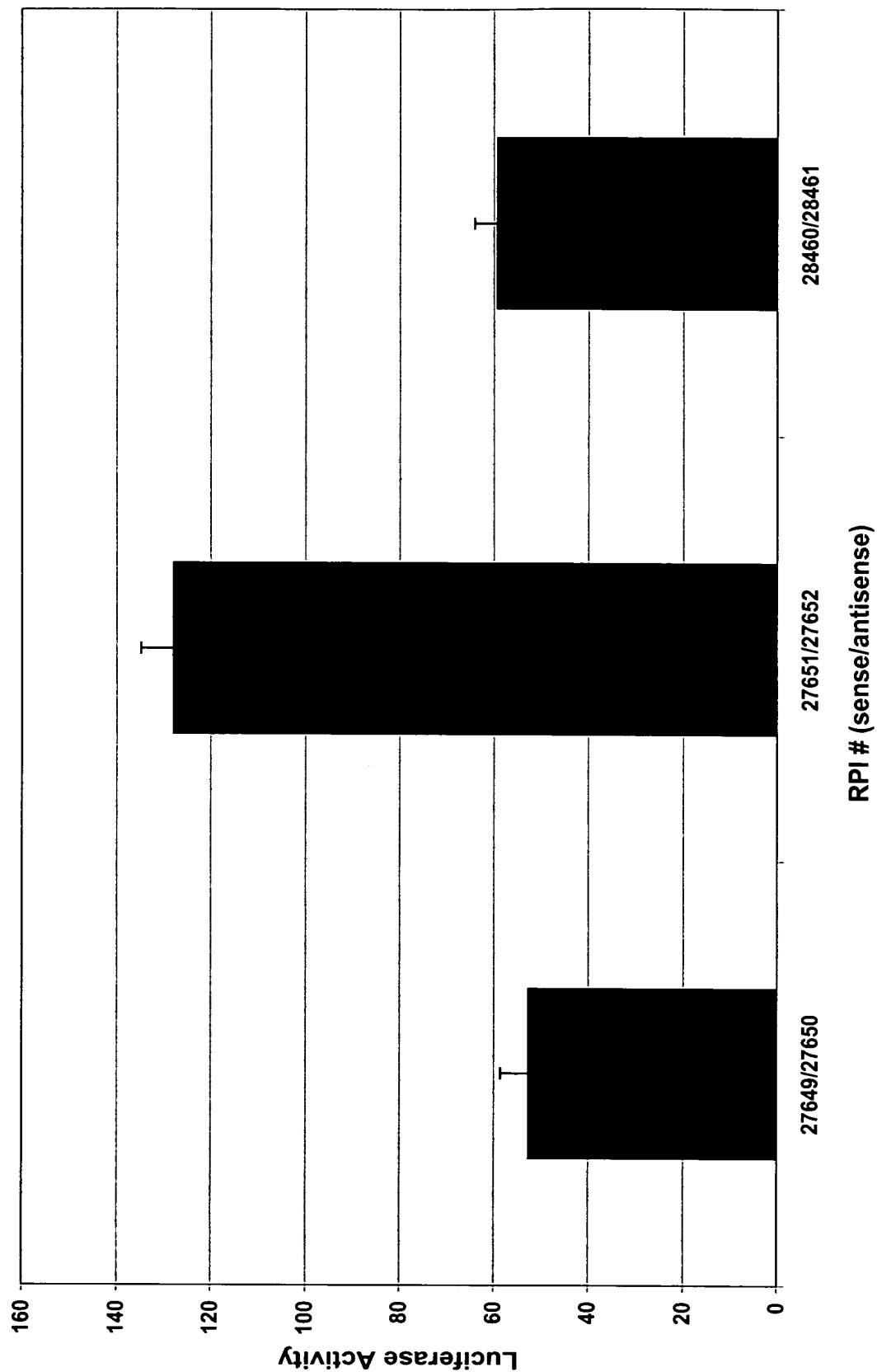


Figure 9

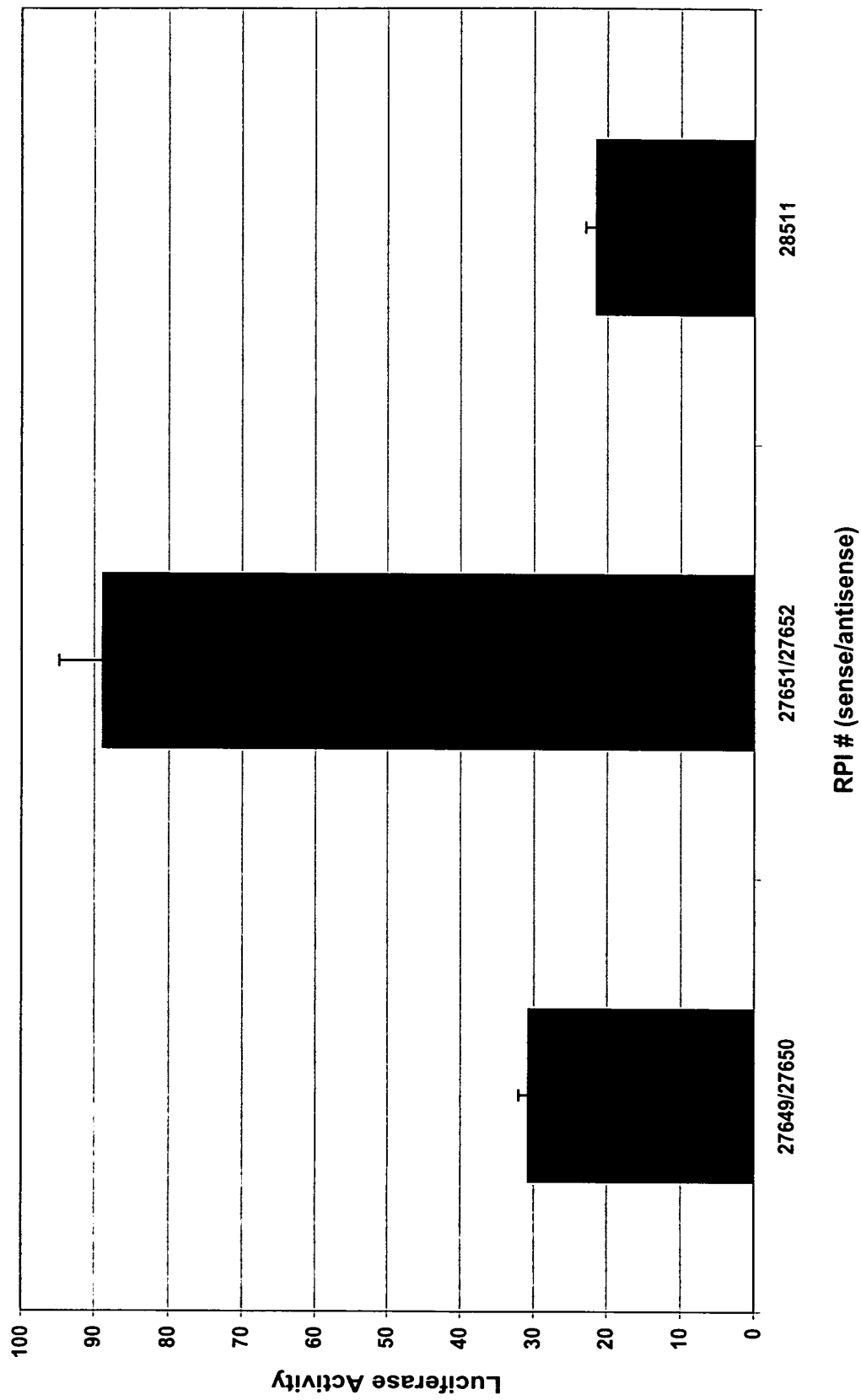


Figure 10

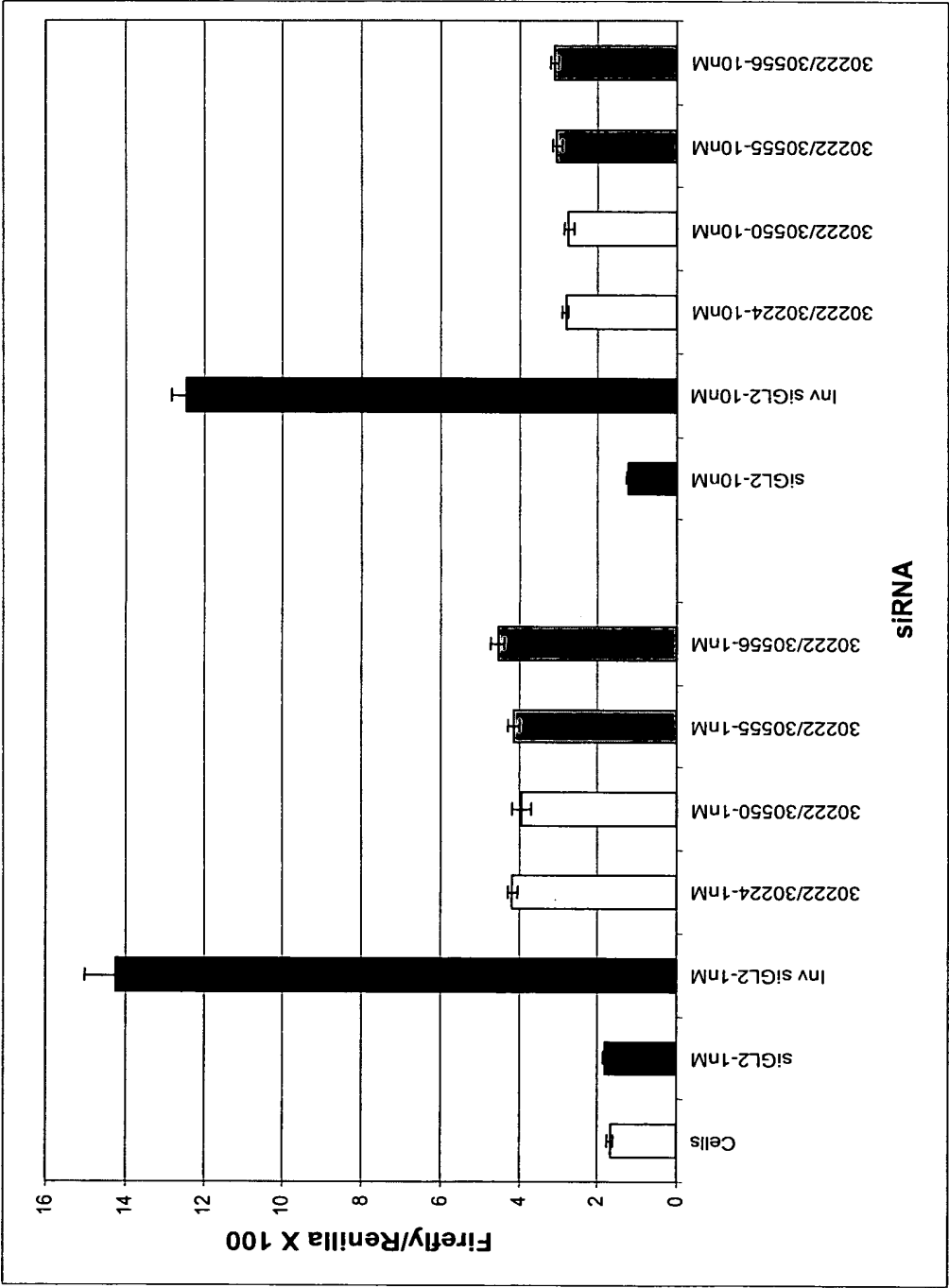


Figure 11

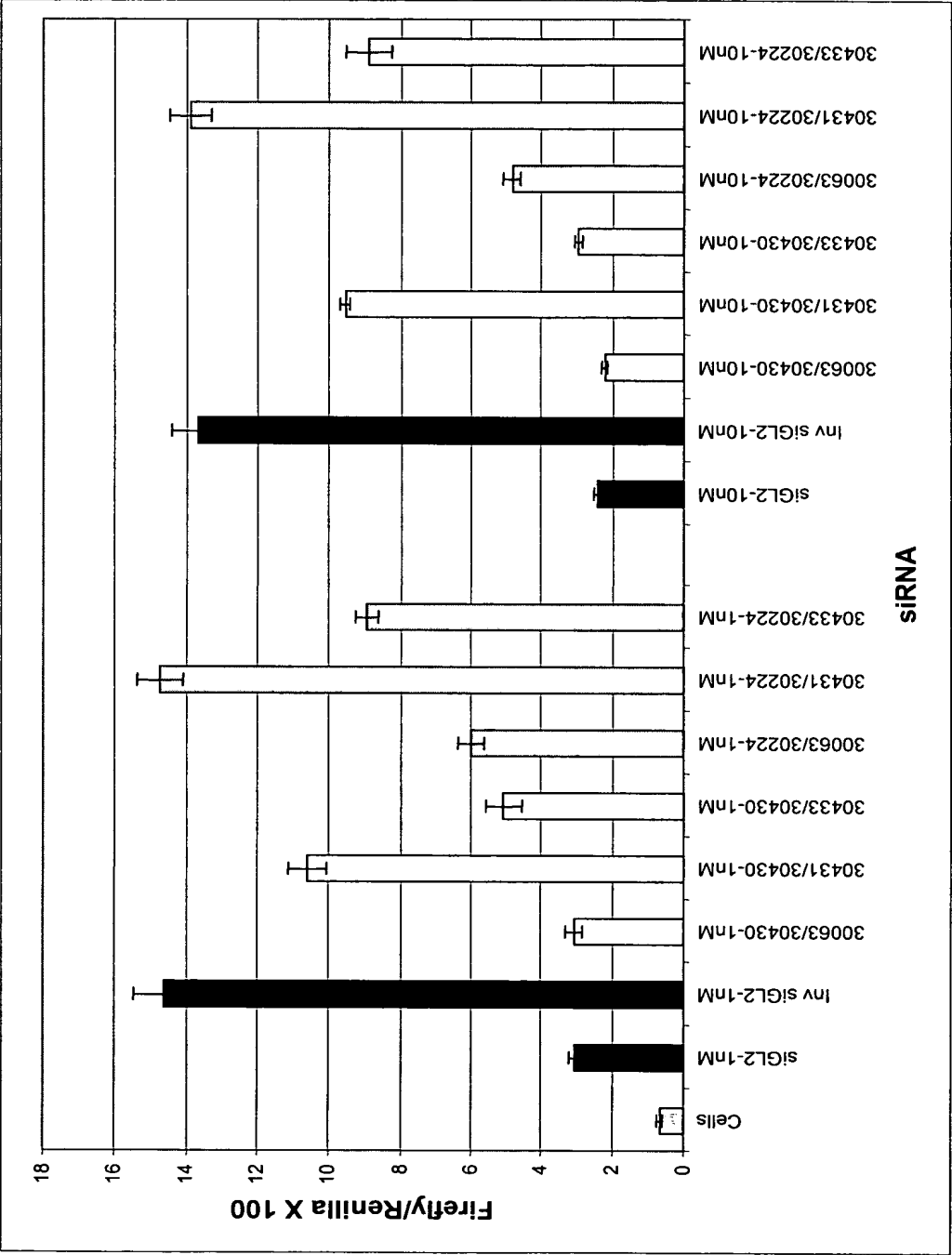


Figure 12

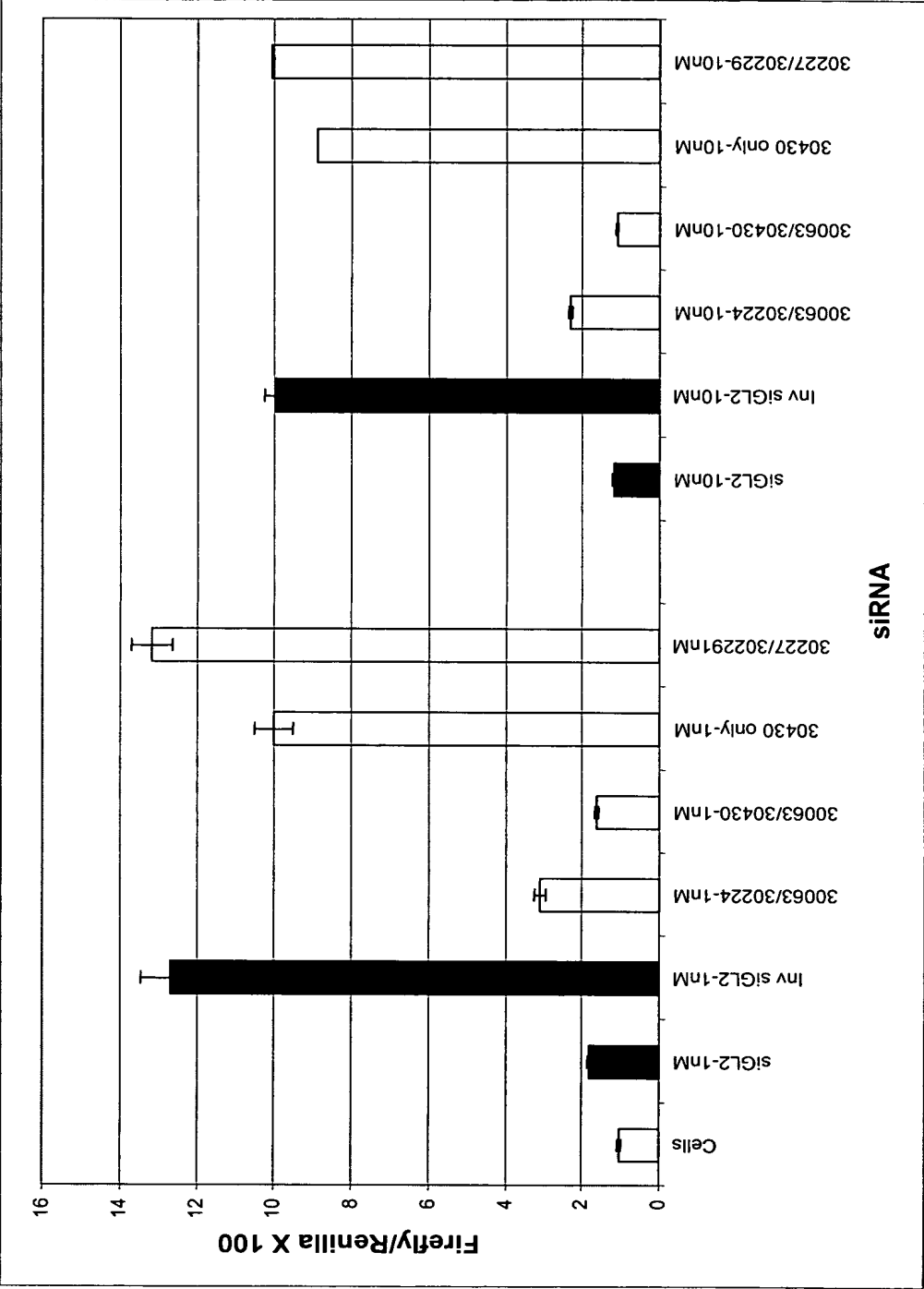


Figure 13

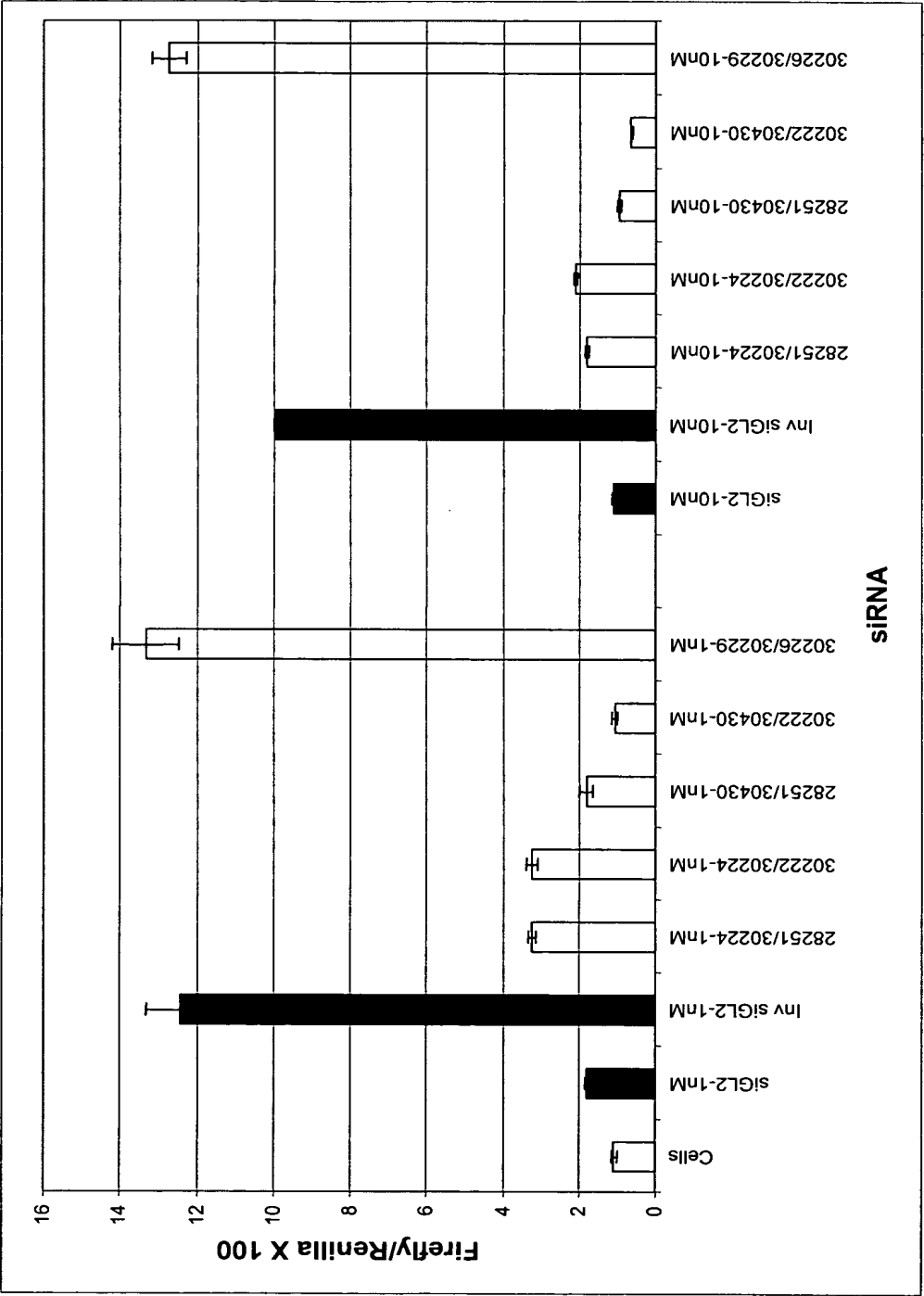


Figure 14

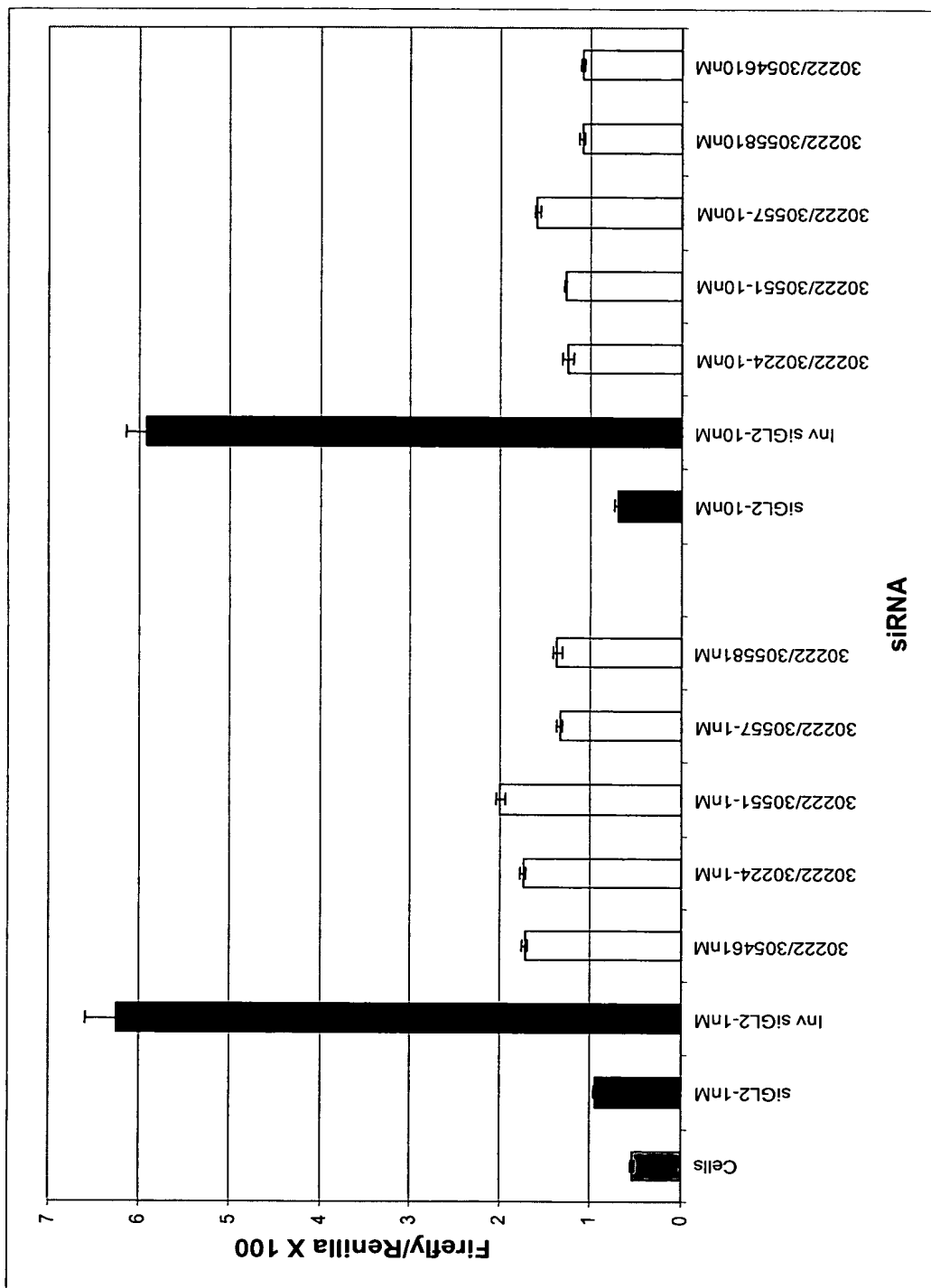


Figure 15

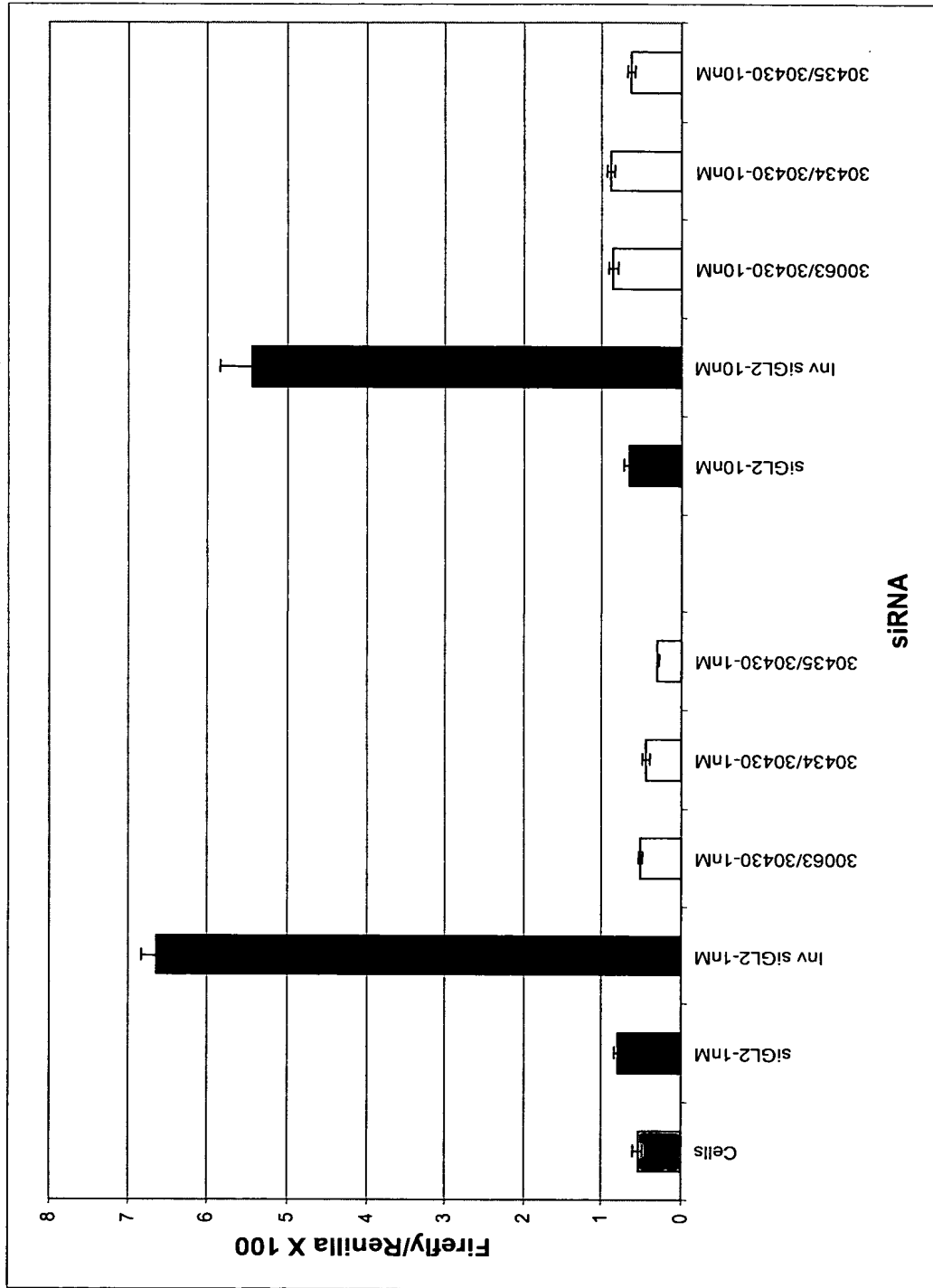


Figure 16

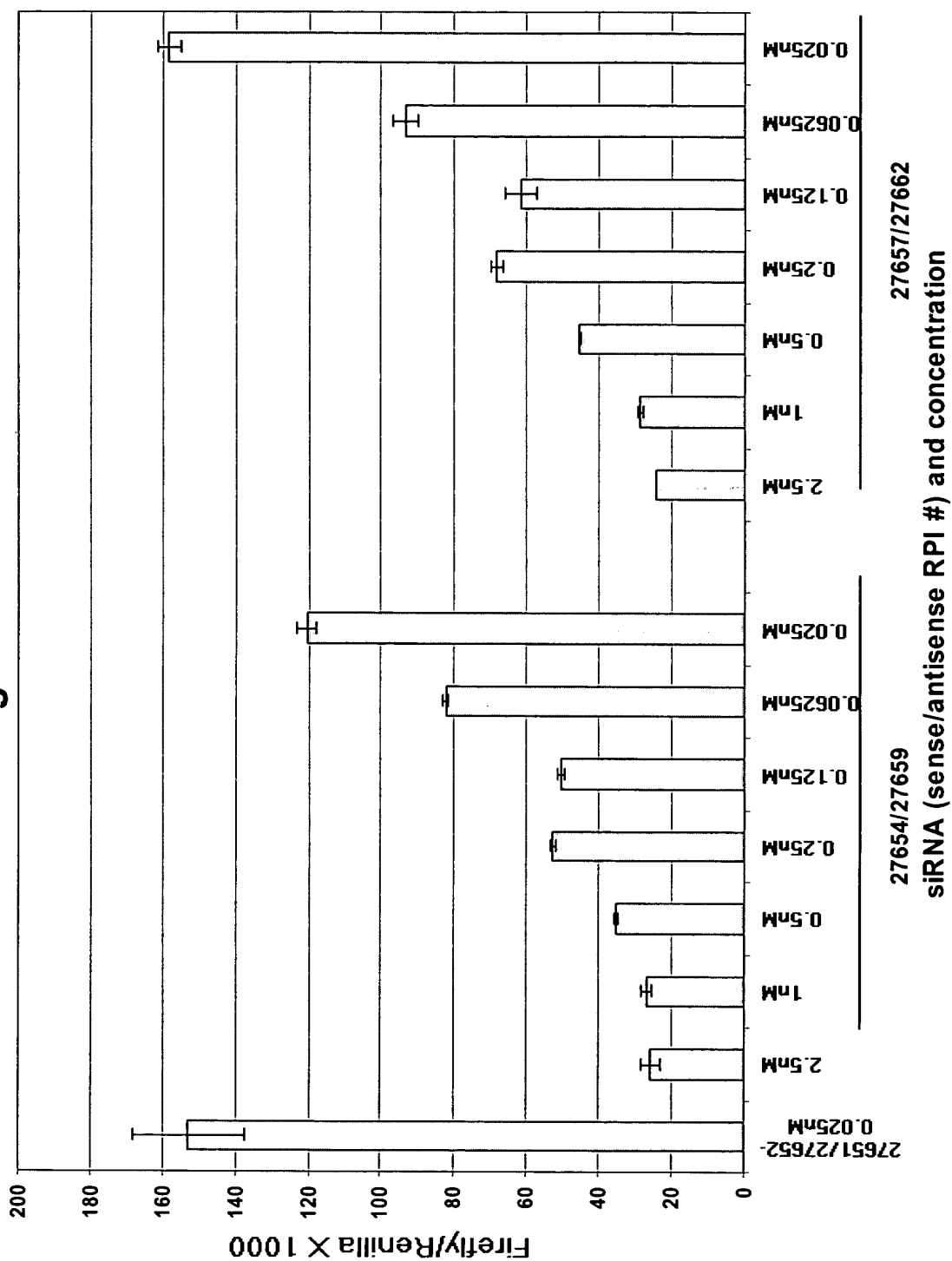


Figure 17

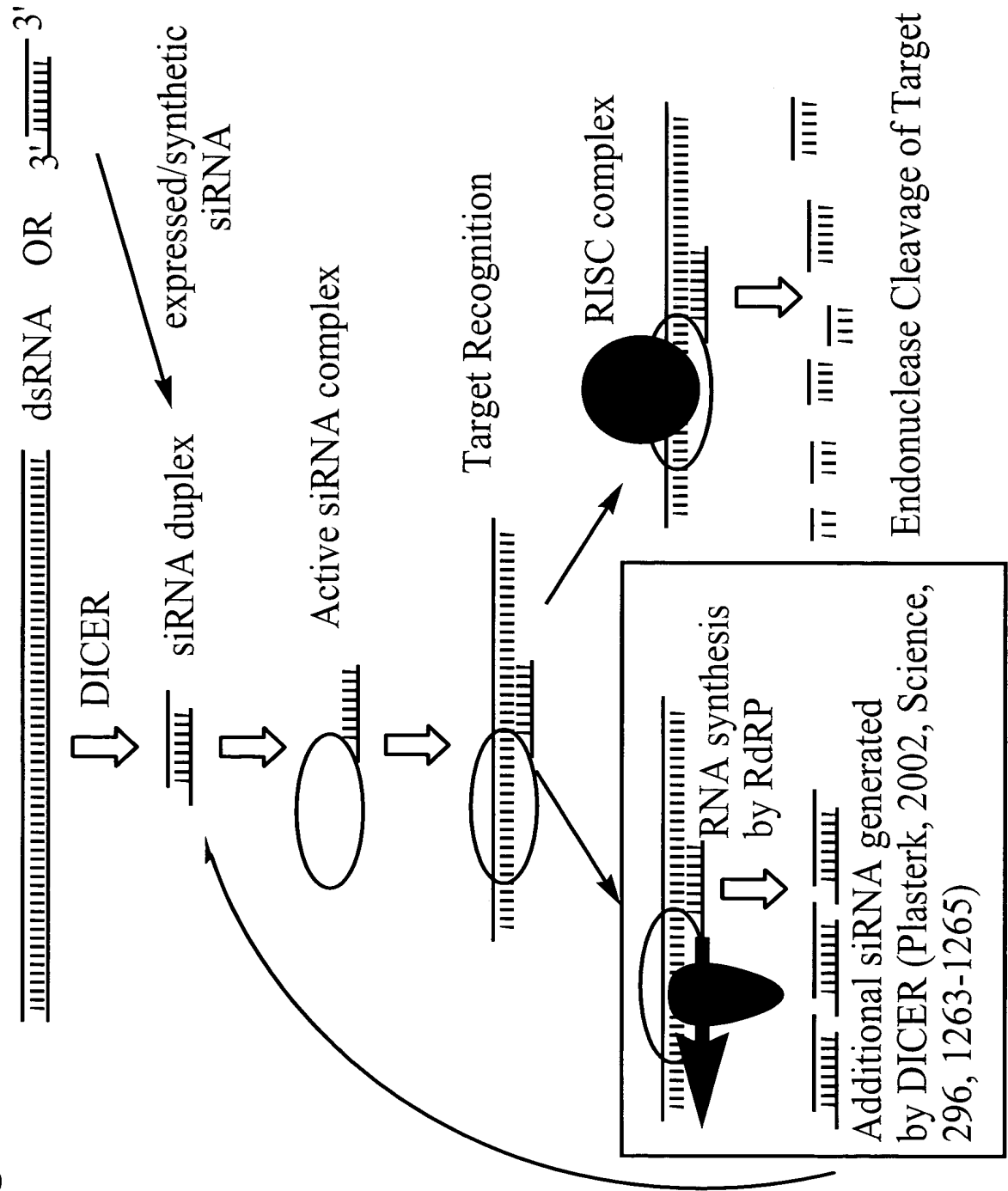
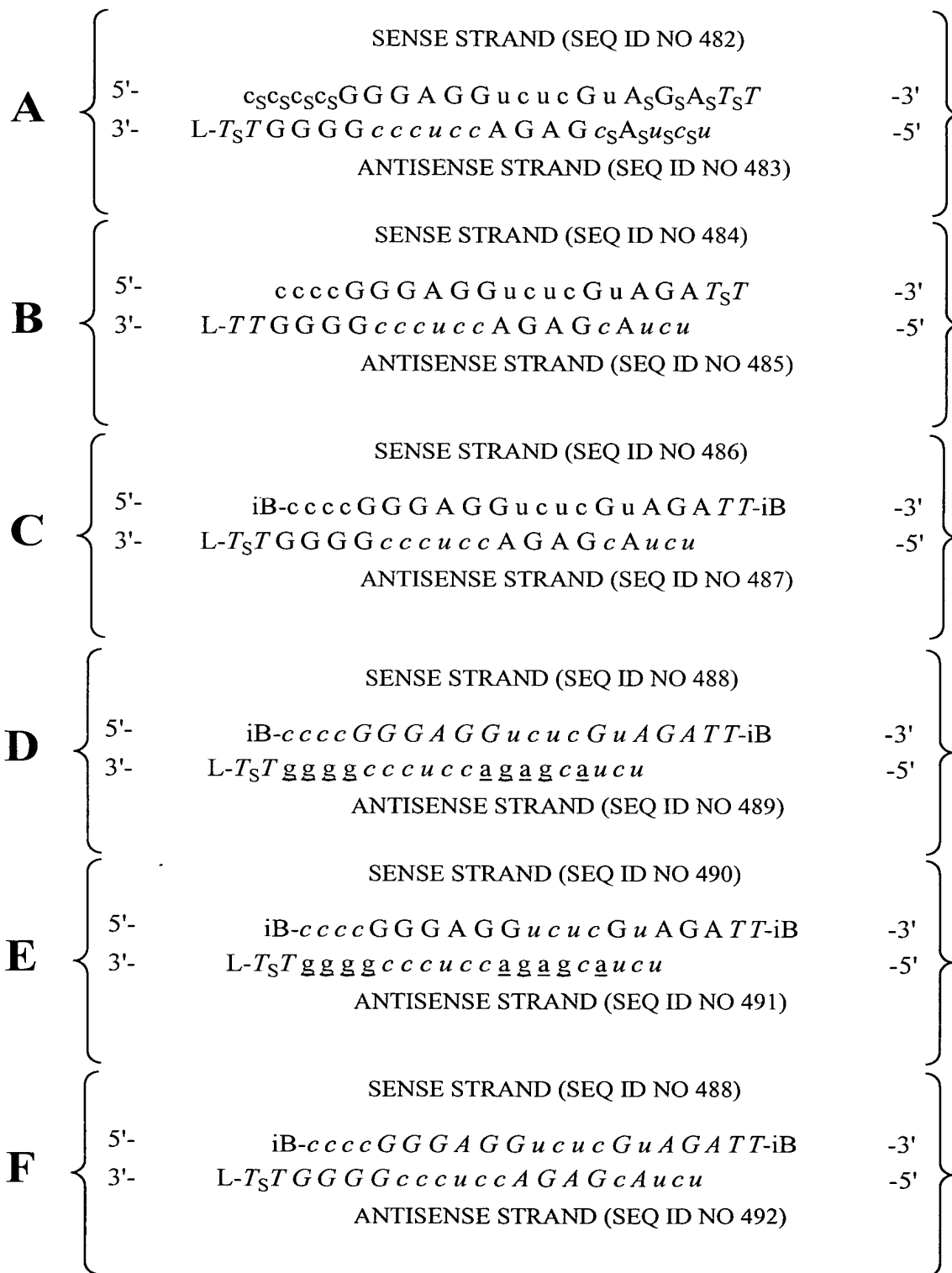


Figure 18



POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES
 B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENT
 L = GLYCERYL or B THAT IS OPTIONALLY PRESENT
 S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE that is optionally absent

Figure 19



lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro

italic lower case = 2'-deoxy-2'-fluoro

underline = 2'-O-methyl

ITALIC UPPER CASE = DEOXY

iB = INVERTED DEOXYABASIC

L = GLYCERYL MOIETY or iB OPTIONALLY PRESENT

S = PHOSPHOROTHIOATE OR

PHOSPHORODITHIOATE OPTIONALLY PRESENT

Figure 20

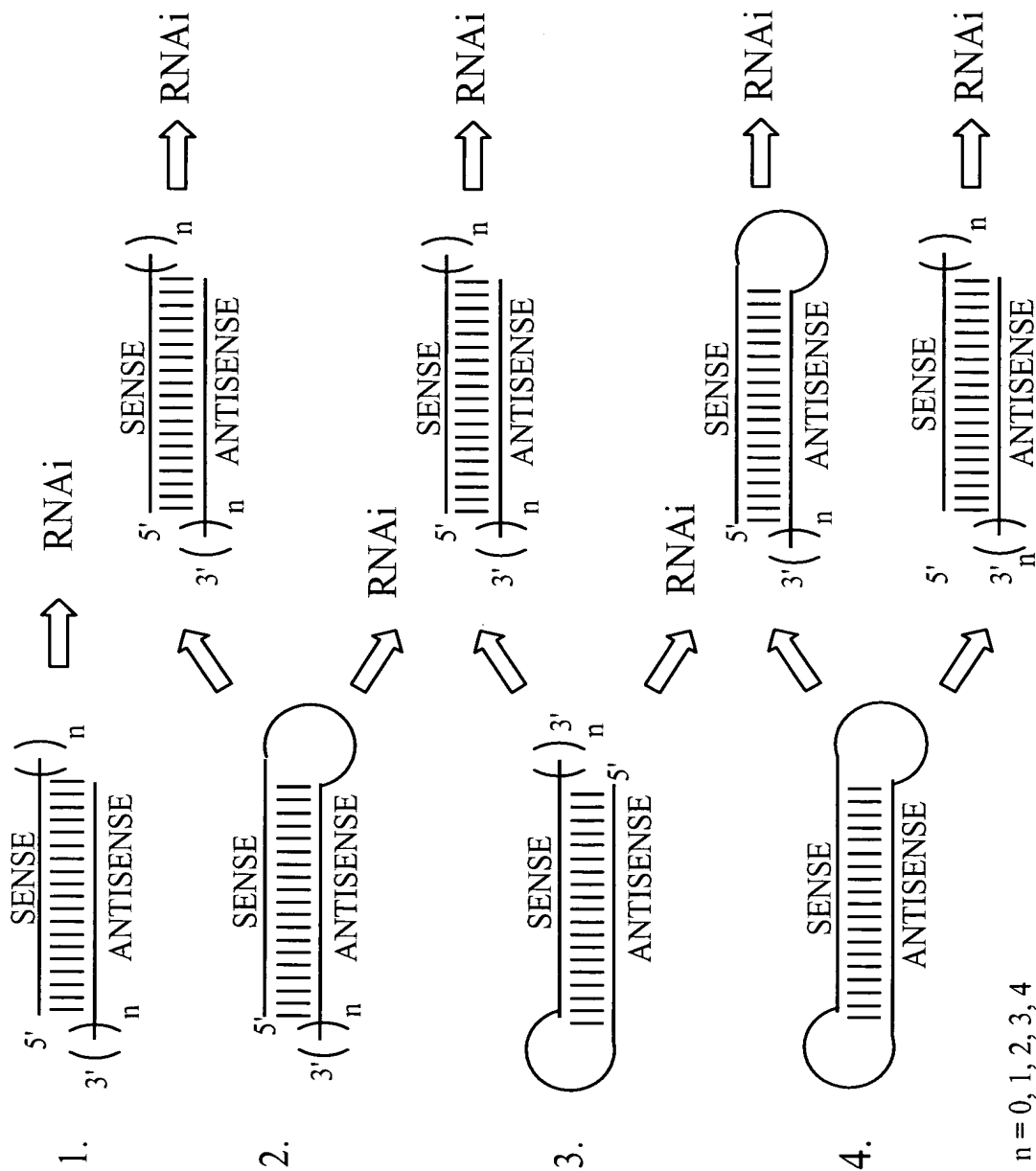


Figure 21: Target site Selection using siRNA

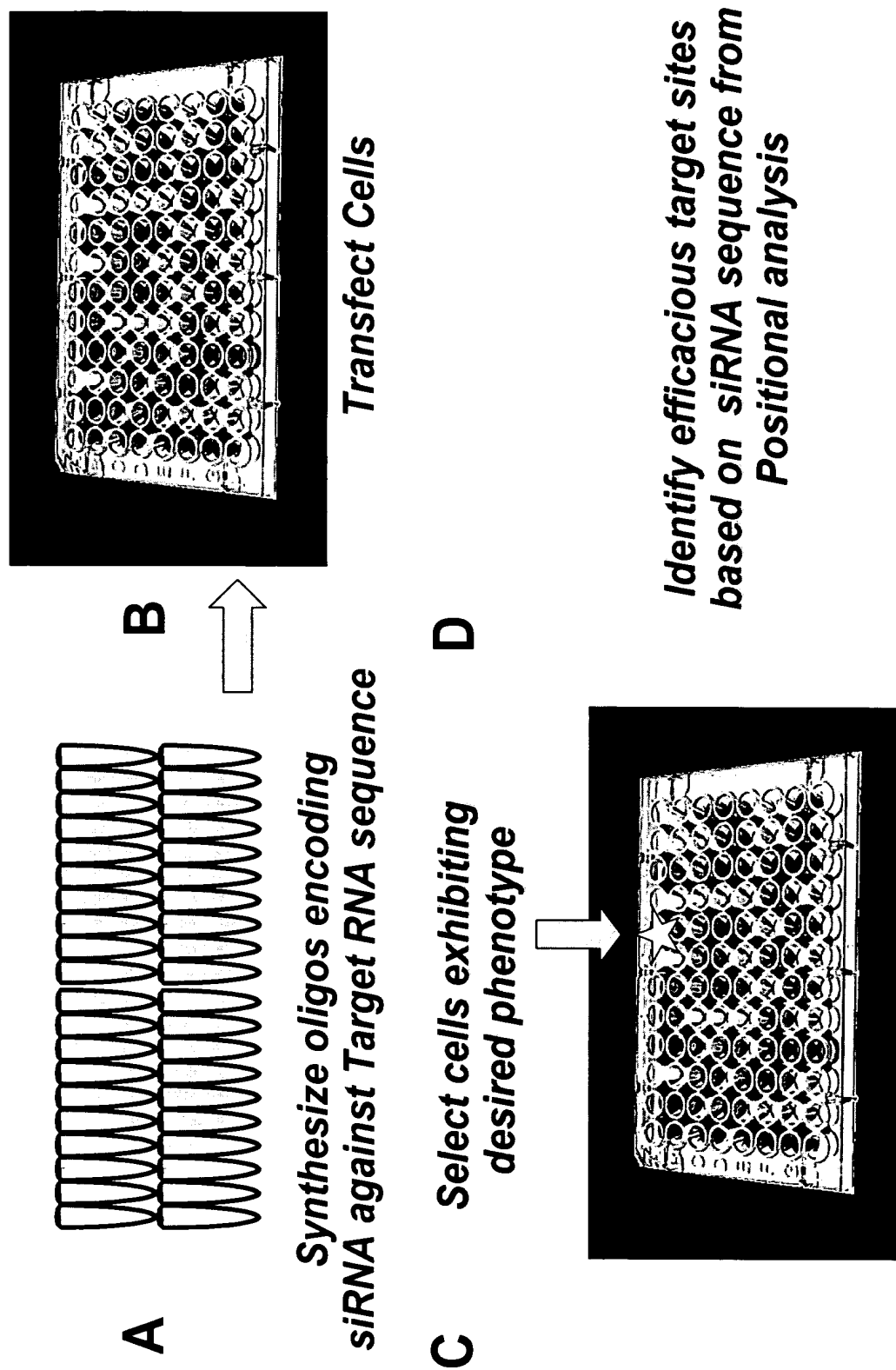
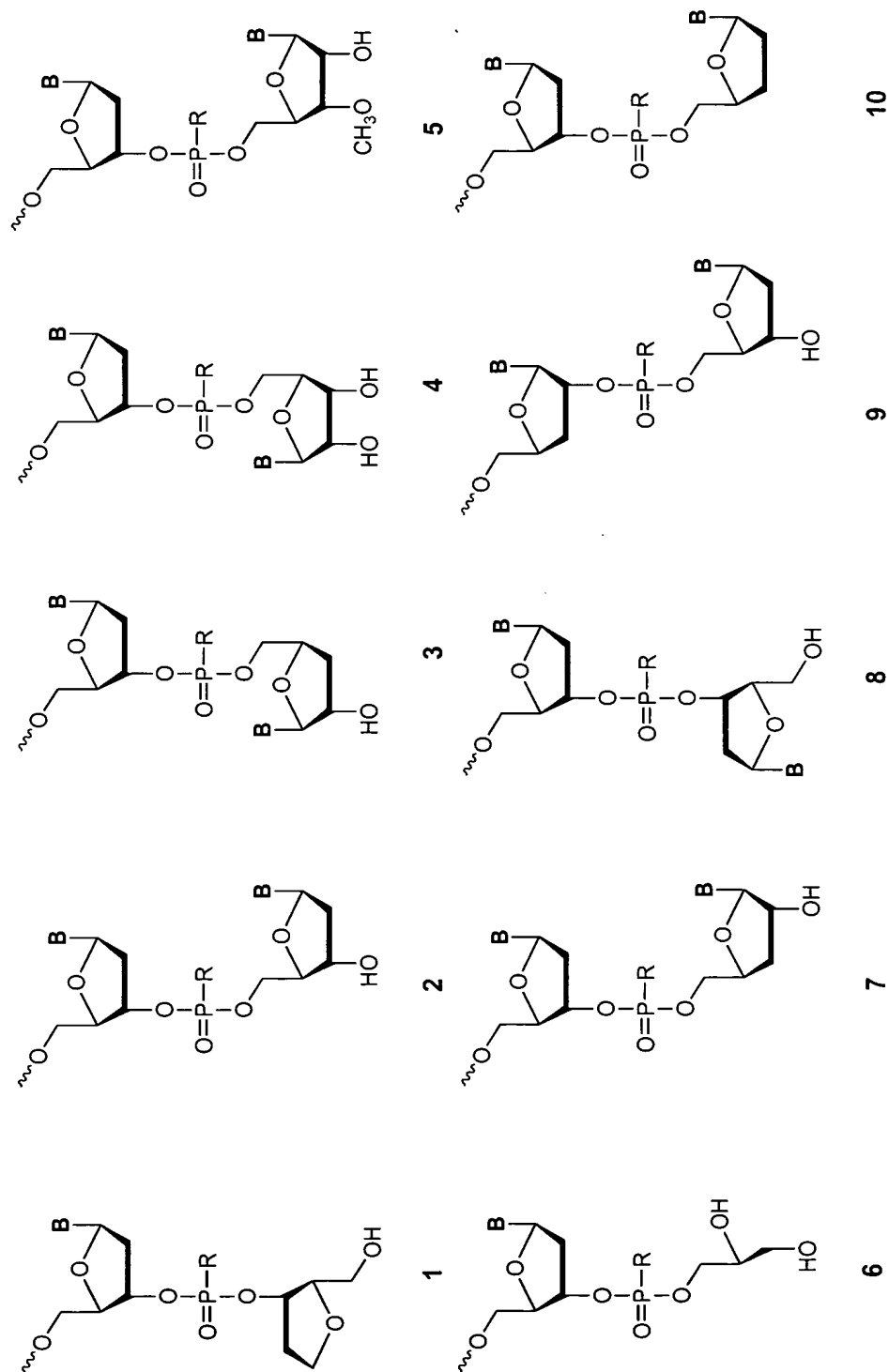
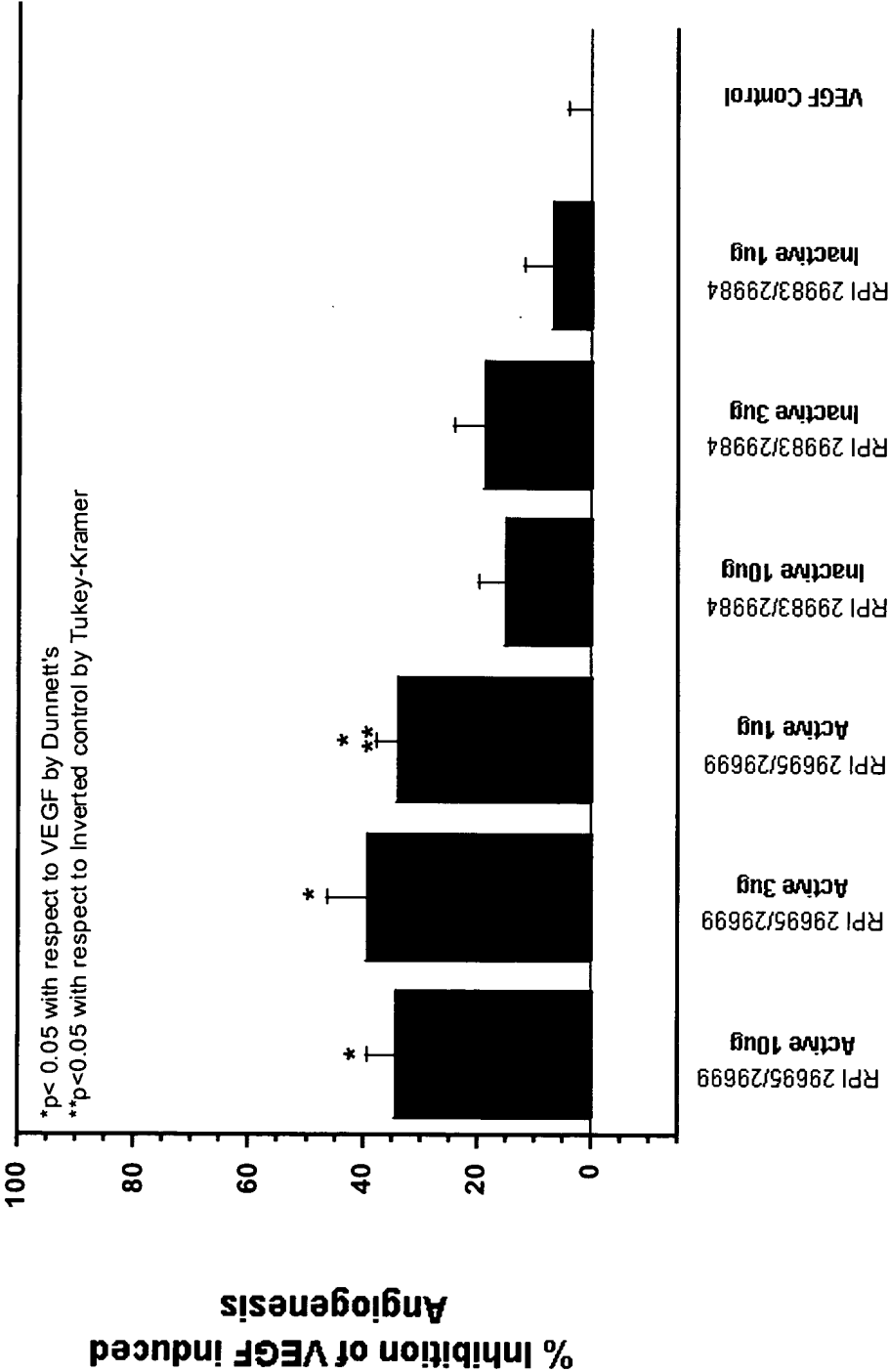


Figure 22



R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl
 B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

**Figure 23: Inhibition of VEGF-Induced Angiogenesis
by siRNAs**



**Figure 24: Stab4/5 siNA Targeted to HBV:
HBsAg Levels in Hep G2 Cells**

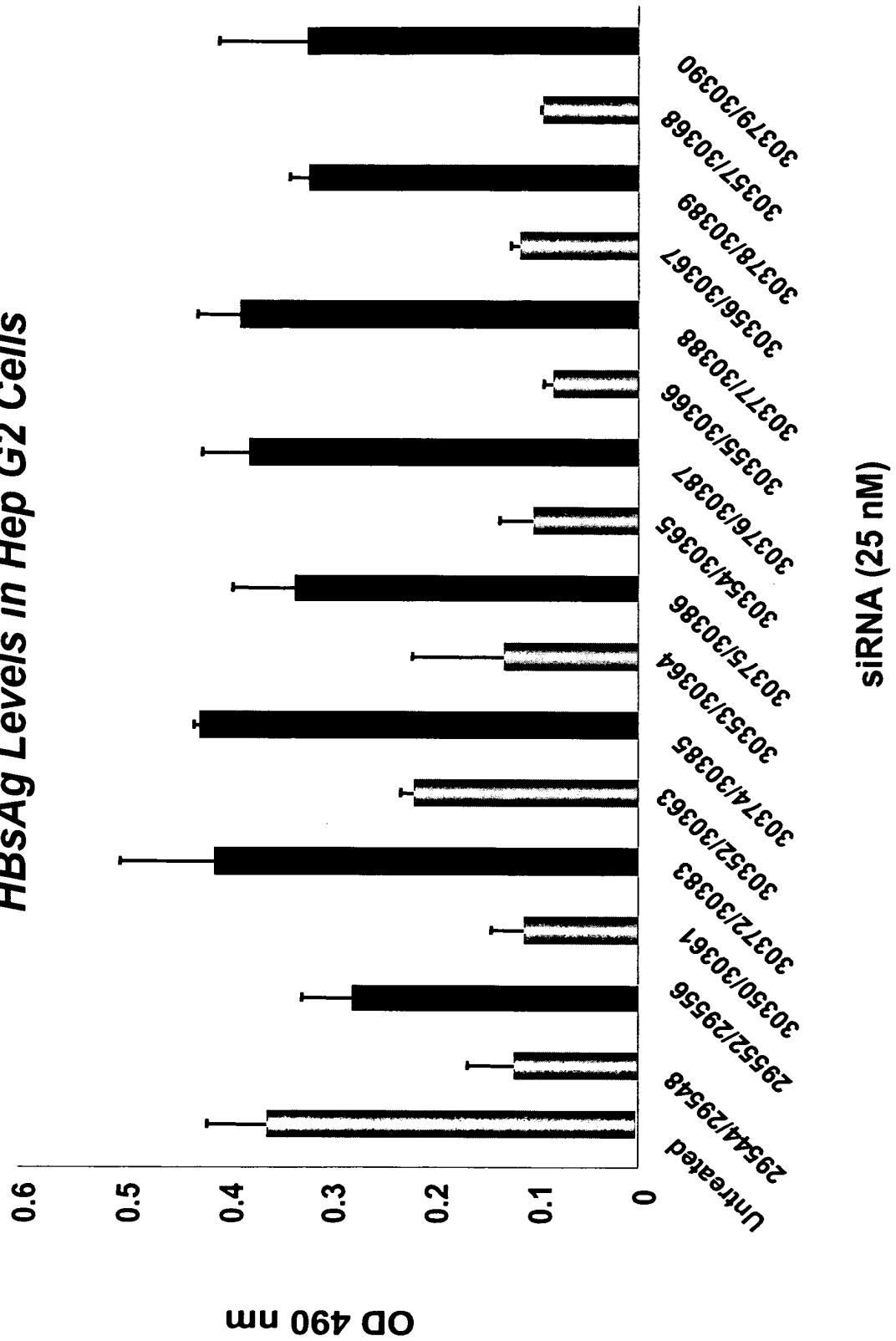


Figure 25: Dose Response with Stab4/5 siRNAs Targeted to HBV Sites 262 & 1580

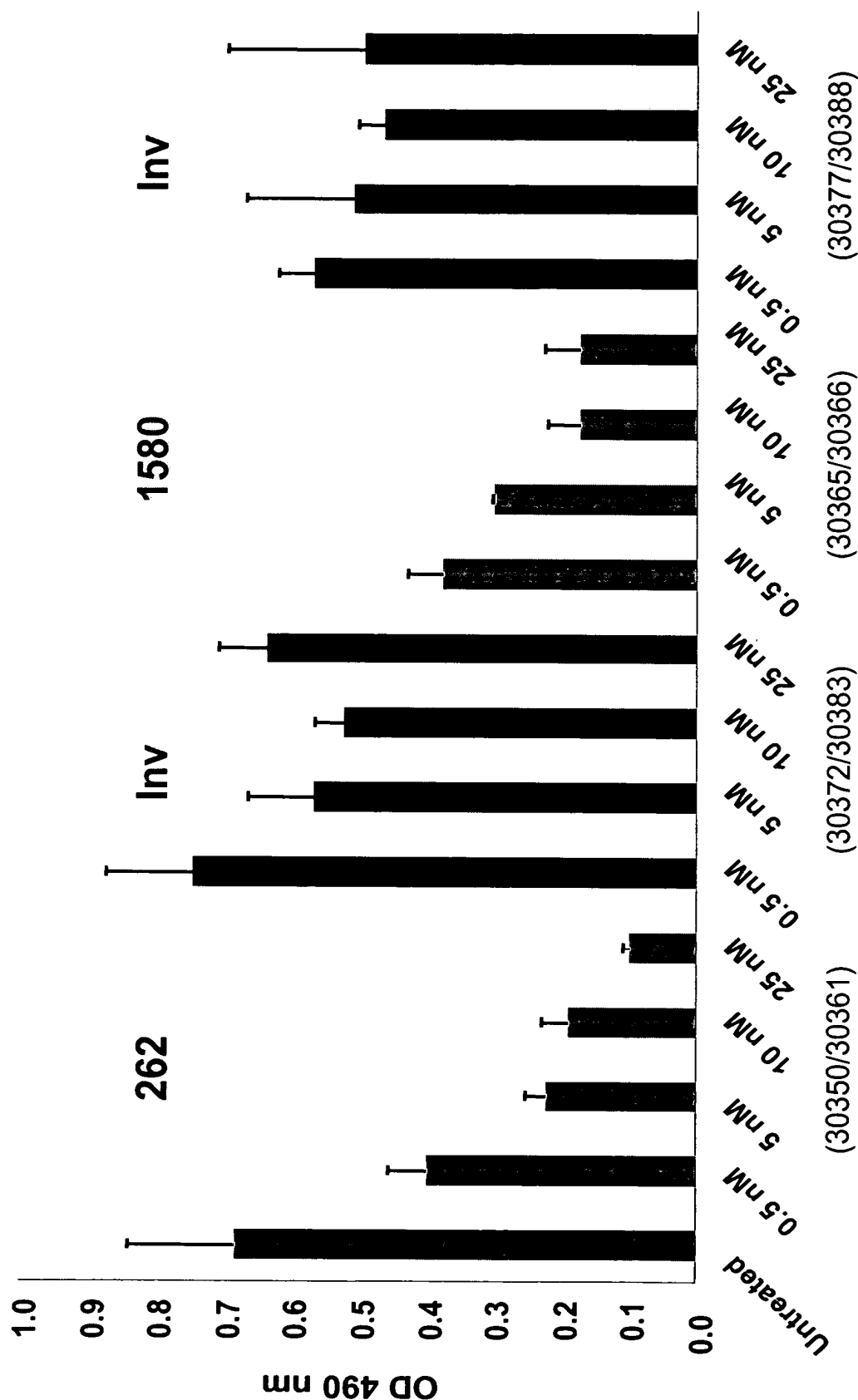


Figure 26: Comparison of Stab7/8 and Stab 7/11 siRNAs Targeted to HBV RNA Site 1580

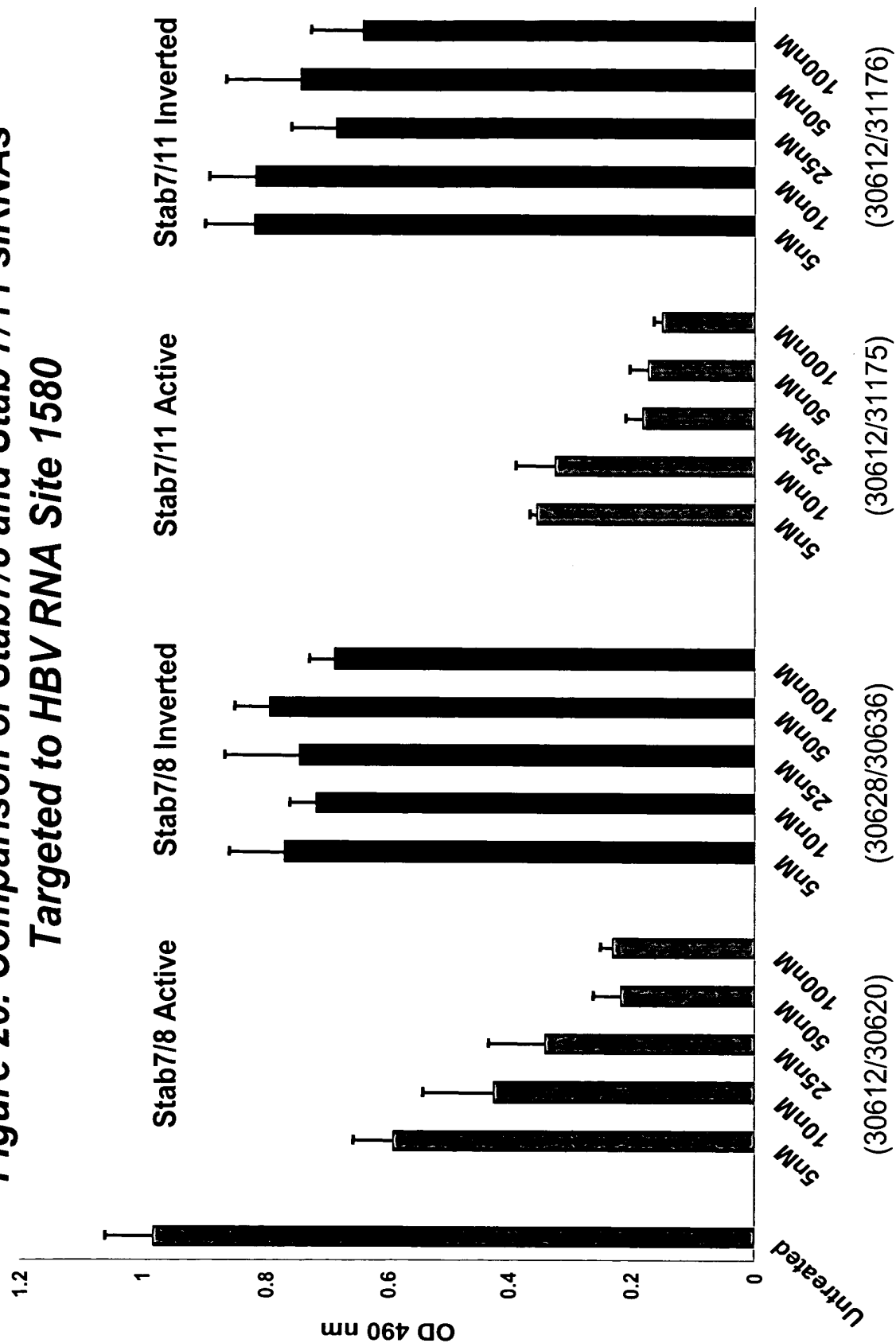


Figure 27: Modification Strategy

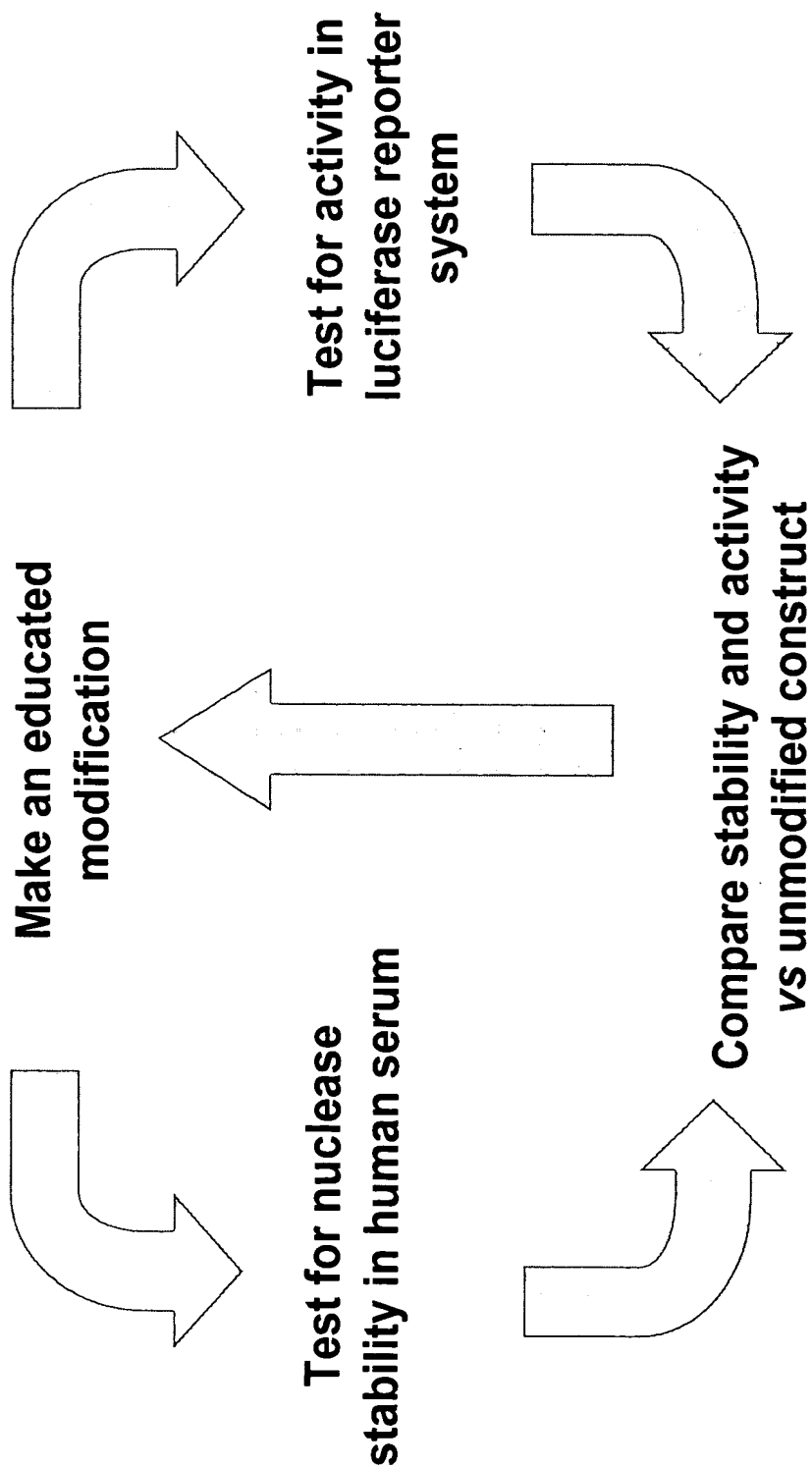


Figure 28: Duration of siRNA Effect
 All-Ribo vs. Stab4/5 HBV Site 1580: HBsAg Levels

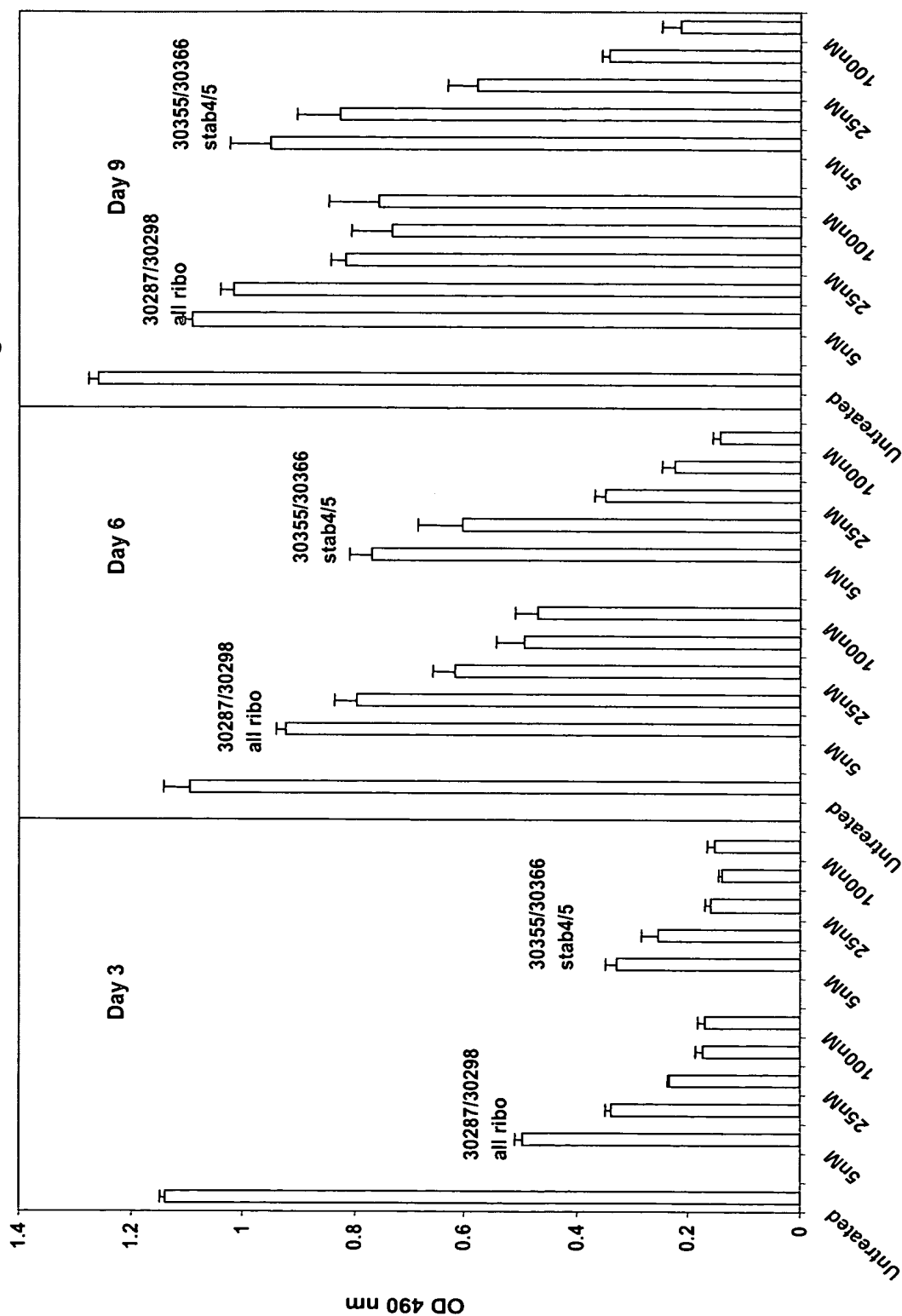


Figure 29: Duration of siRNA Effect
 All-Ribo vs. Stab7/8 HBV Site 1580: HBsAg Levels

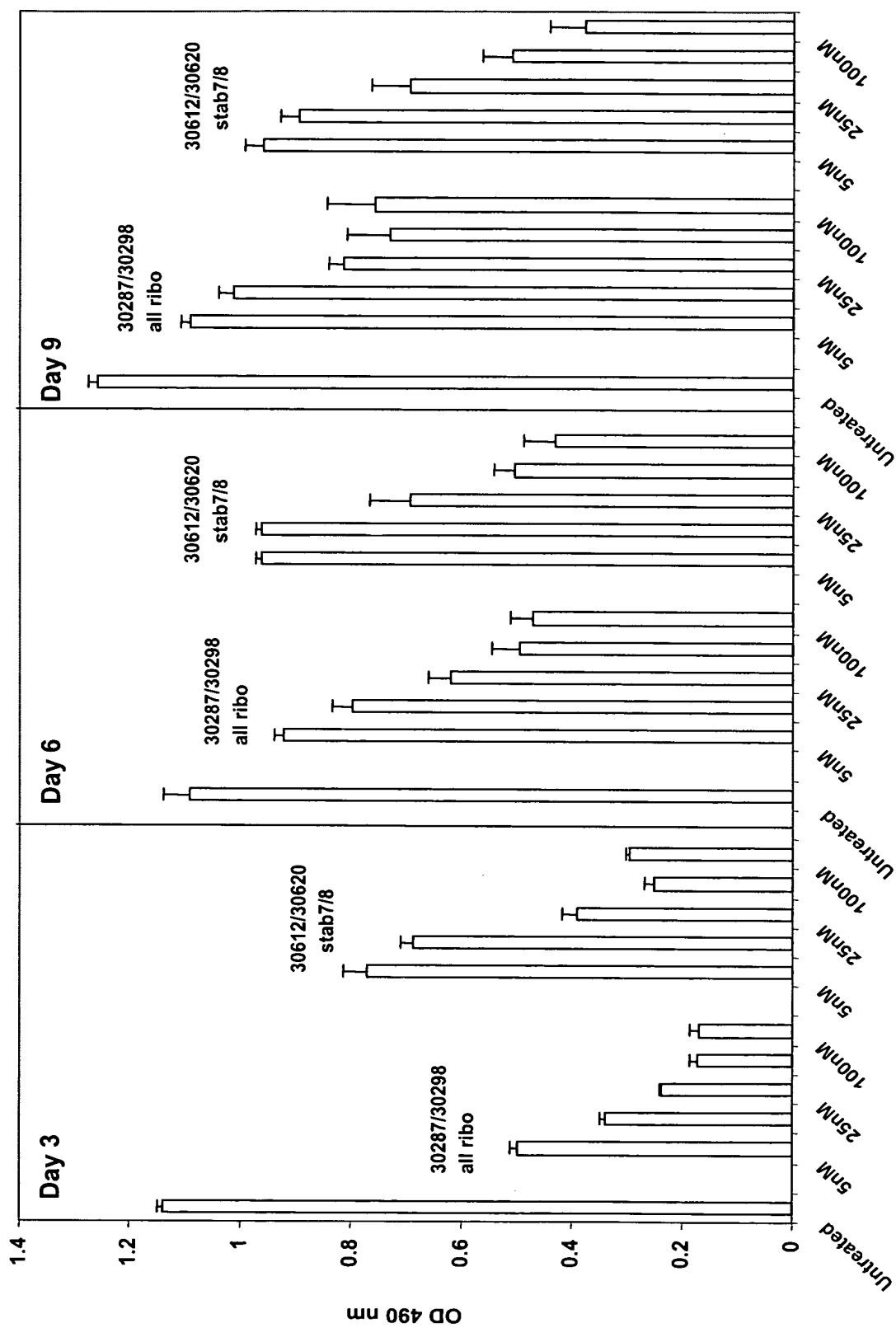


Figure 30: Duration of siRNA Effect
 All-Ribo vs. Stab7/11 HBV Site 1580: HBsAg Levels

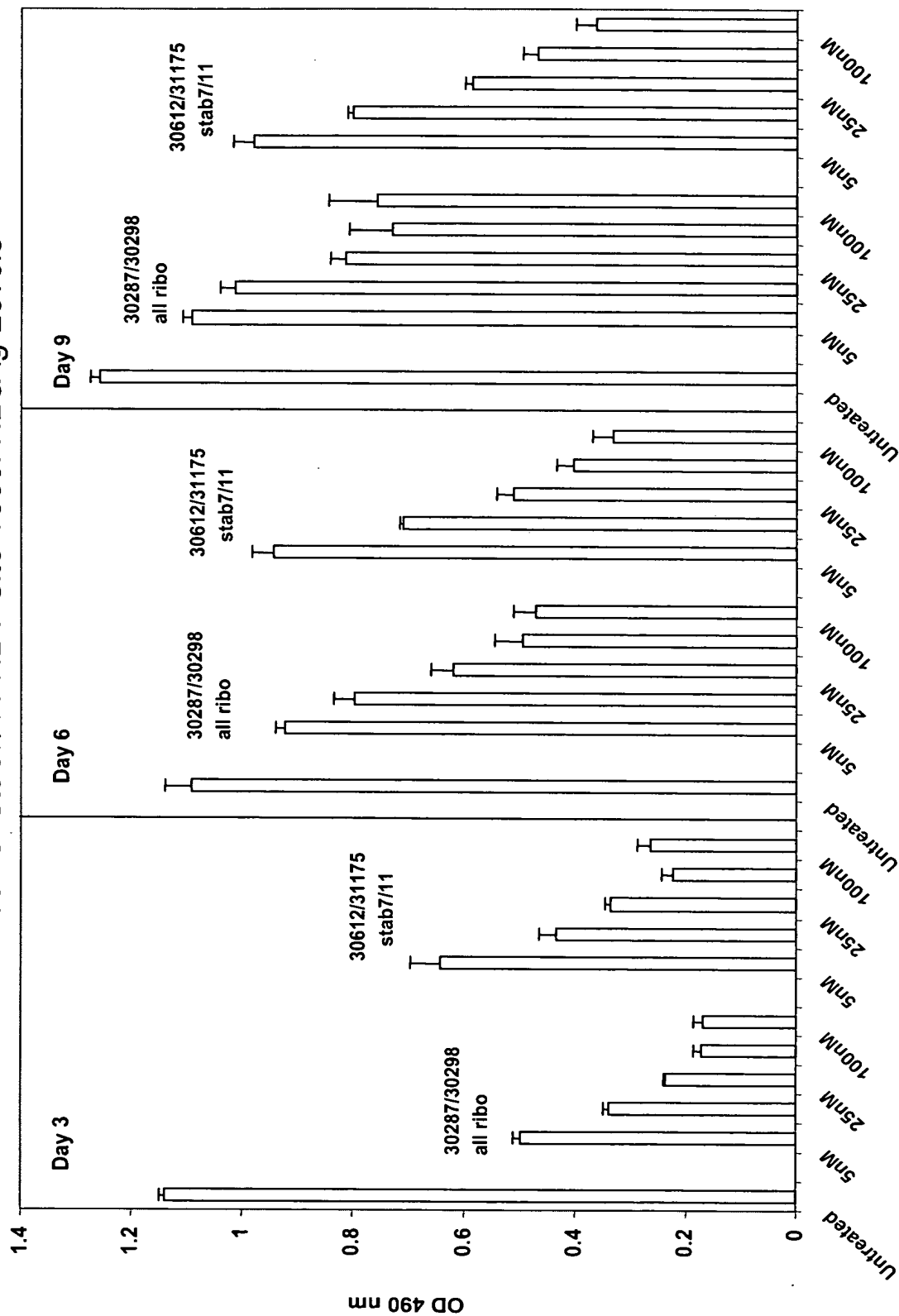


Figure 31: Duration of siRNA Effect
All-Ribo vs. Stab9/10 HBV Site 1580: HBsAg Levels

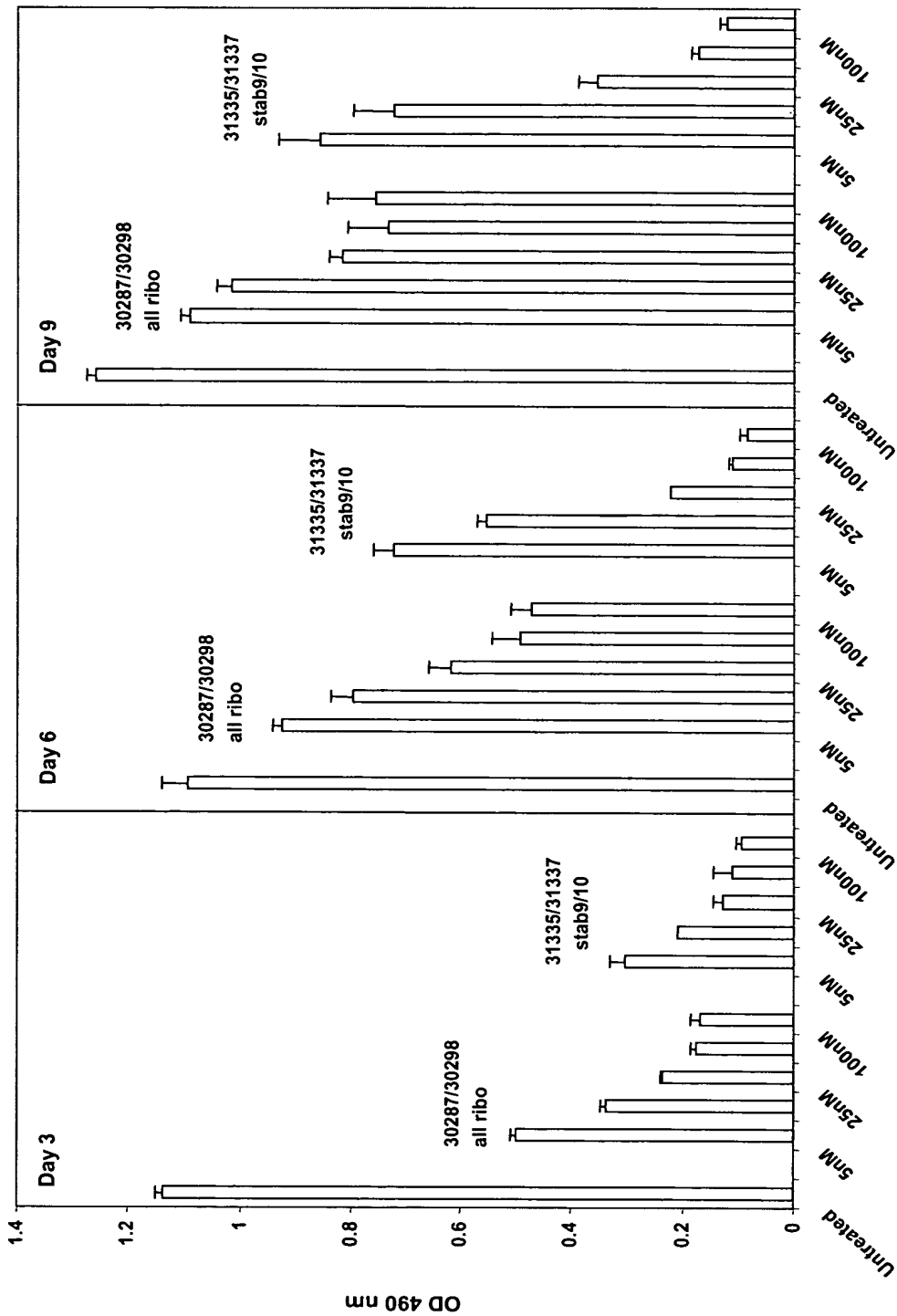


Figure 32 : siRNAs targeting HCV chimera

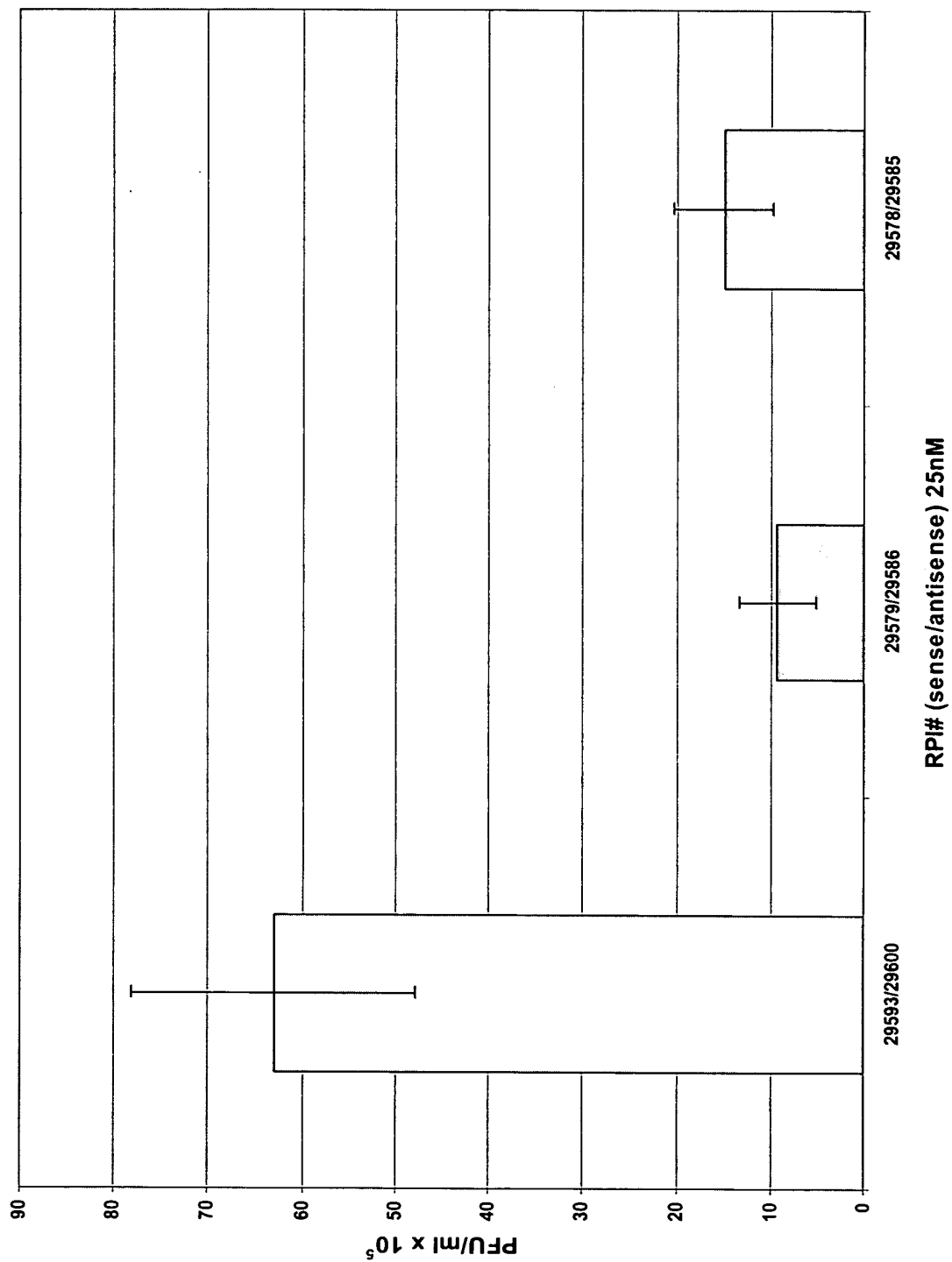
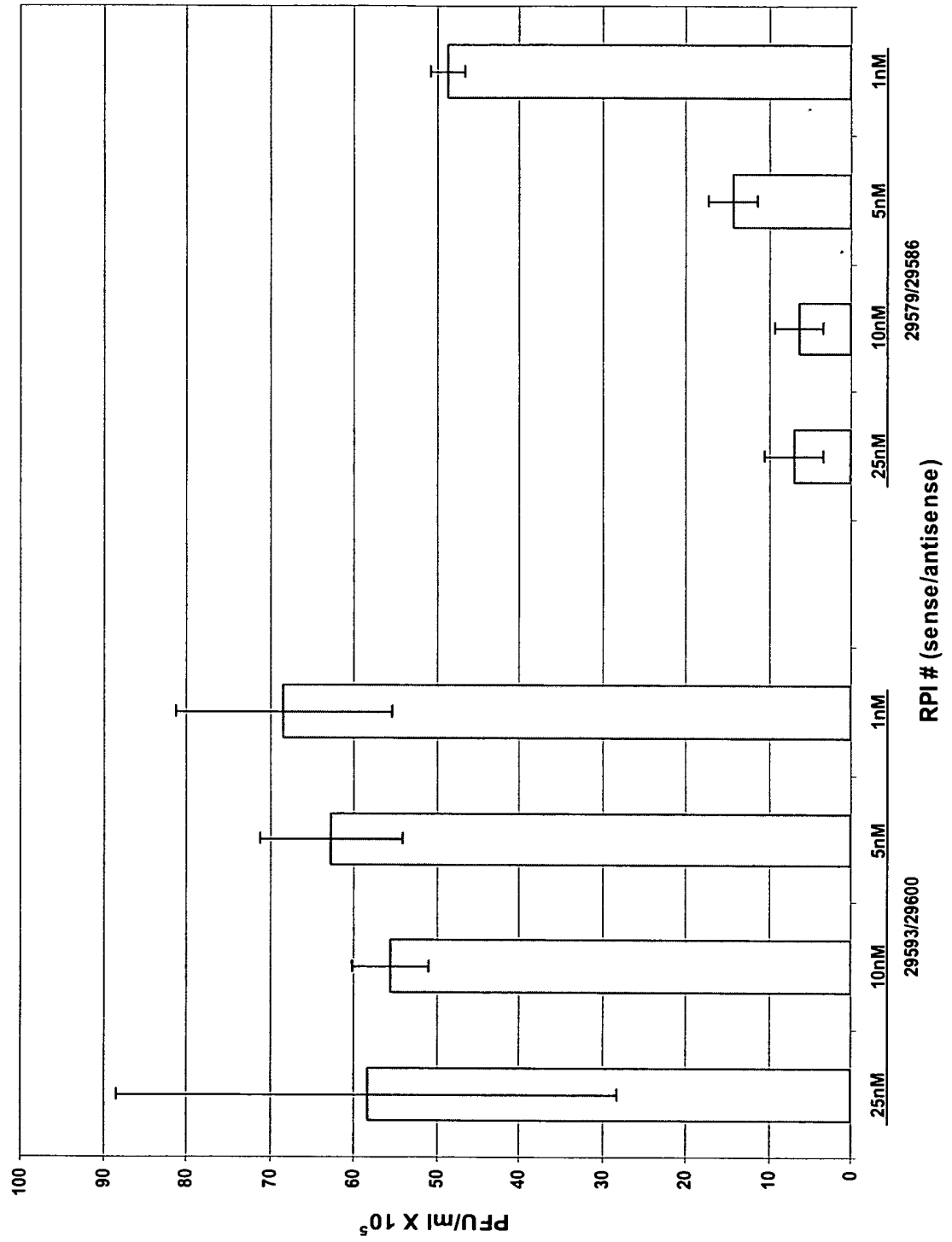
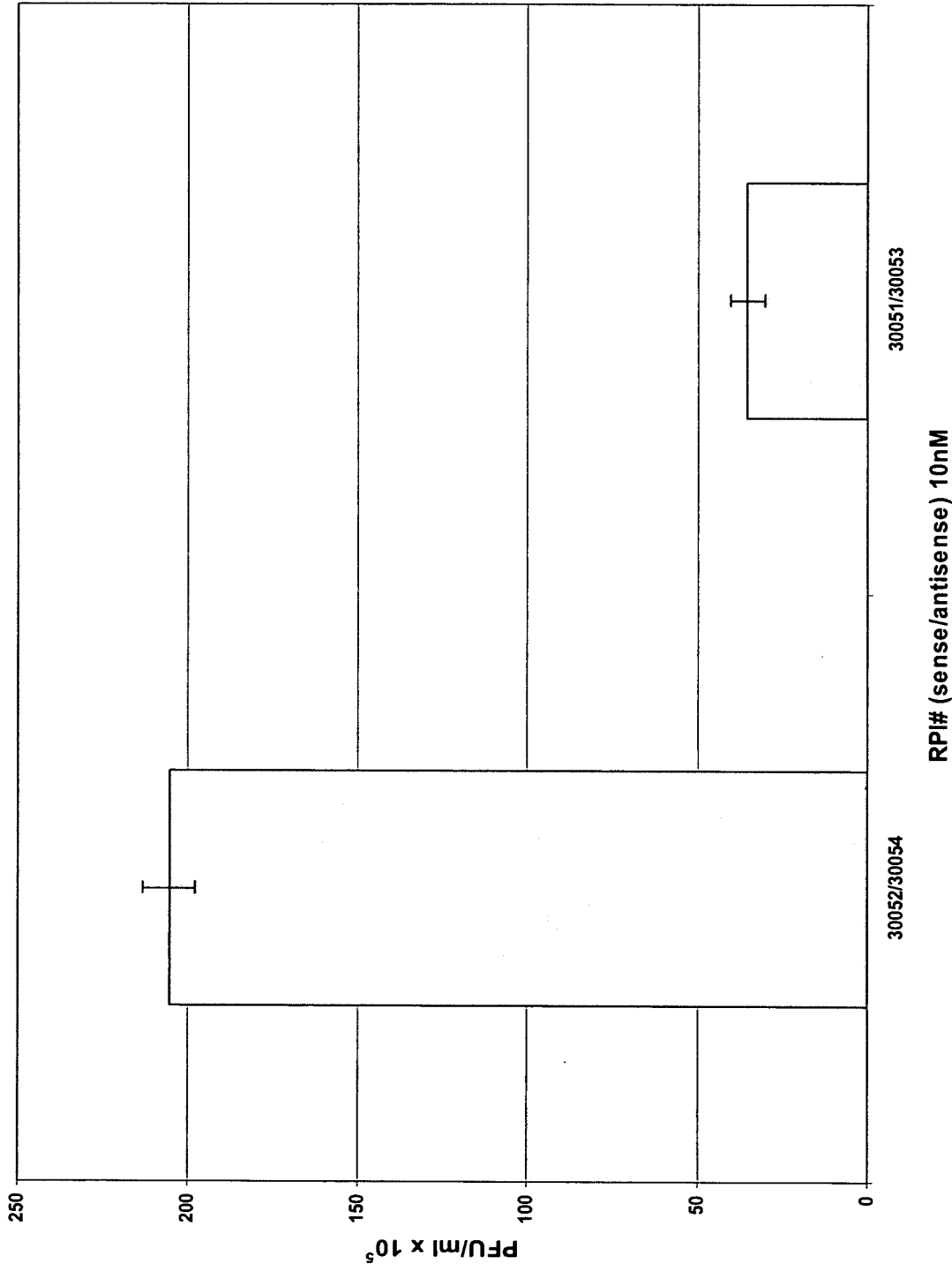


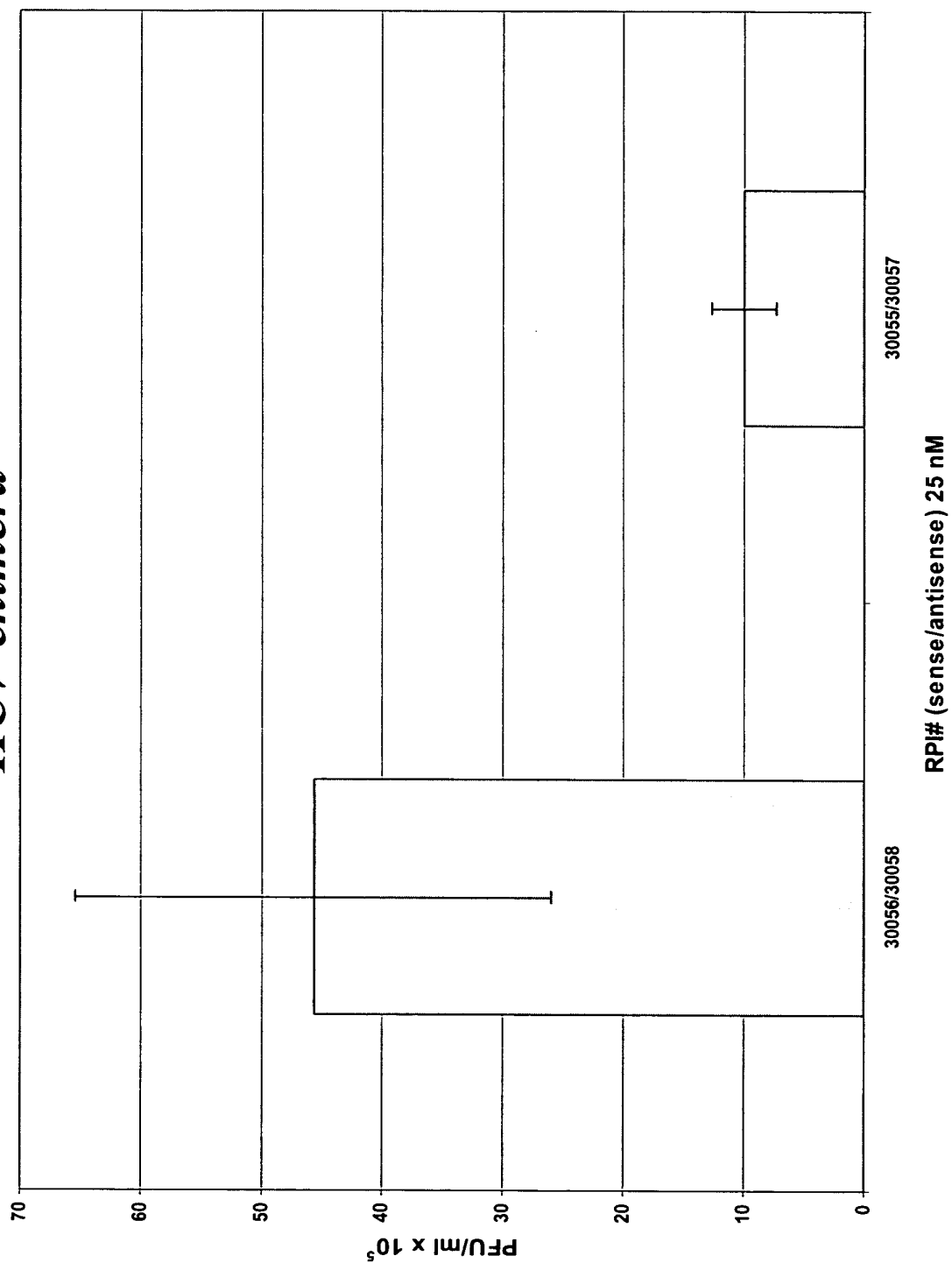
Figure 33: HCV siRNA dose response



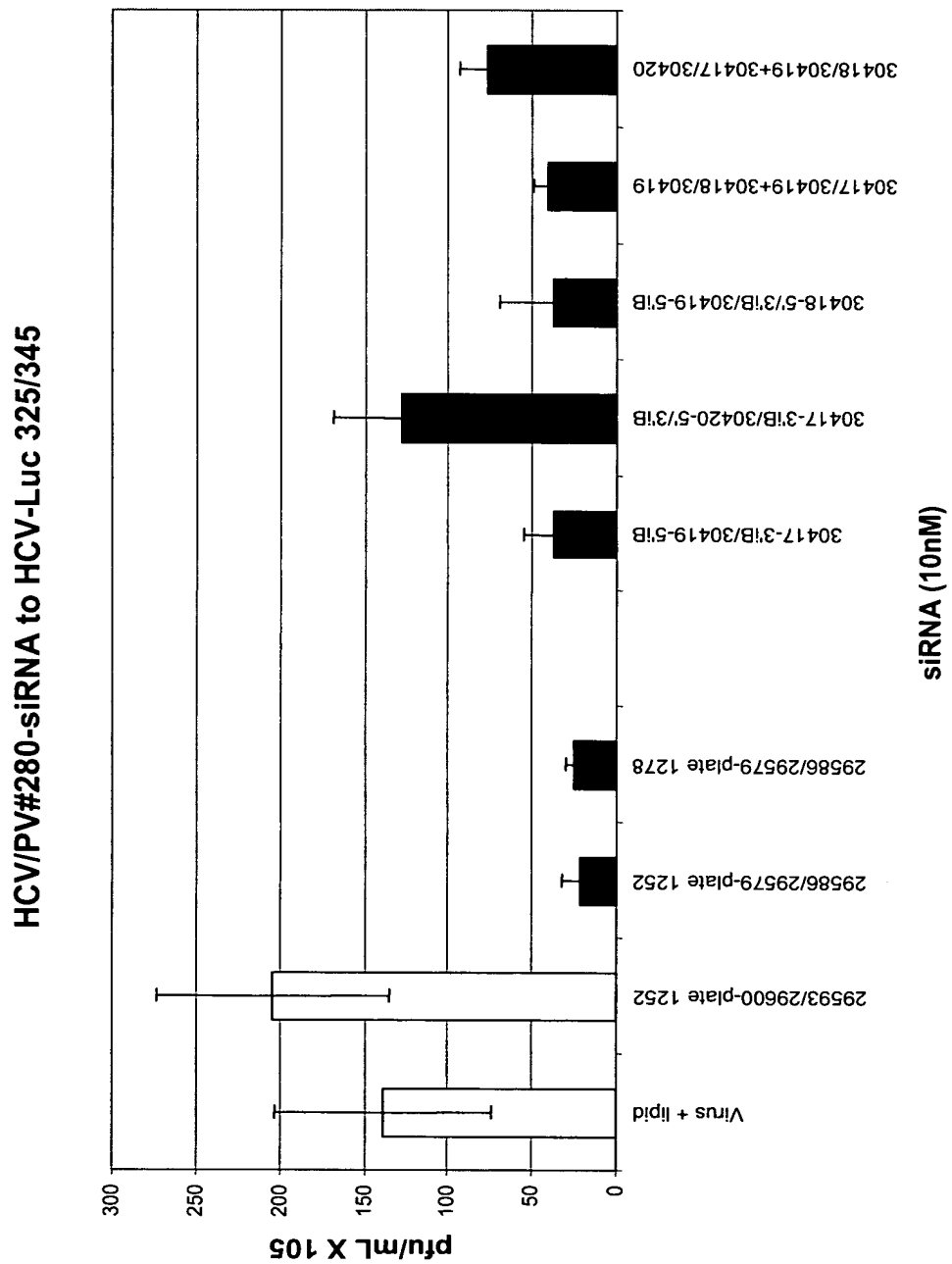
**Figure 34: Chemically Modified siRNA targeting
HCV chimera**



**Figure 35: Chemically Modified siRNA targeting
HCV chimera**

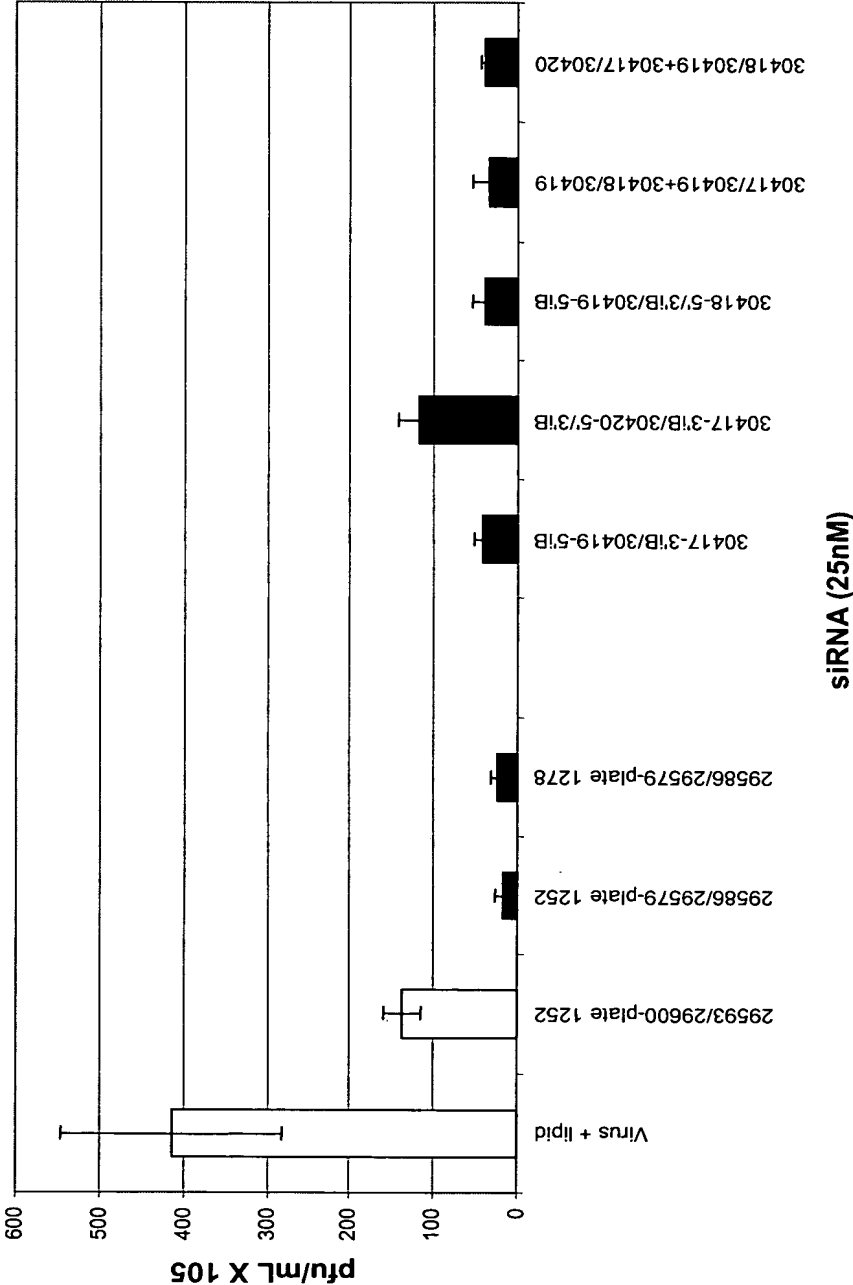


**Figure 36: Chemically Modified siRNA
targeting HCV chimera**



*Figure 37: Chemically Modified siRNA
targeting HCV chimera*

HCV/PV#280-siRNA to HCV-Luc site 325/345



**Figure 38: HCV/Replicon Cells transfected
with 0.5µl/well LFA 2K-72 hours**

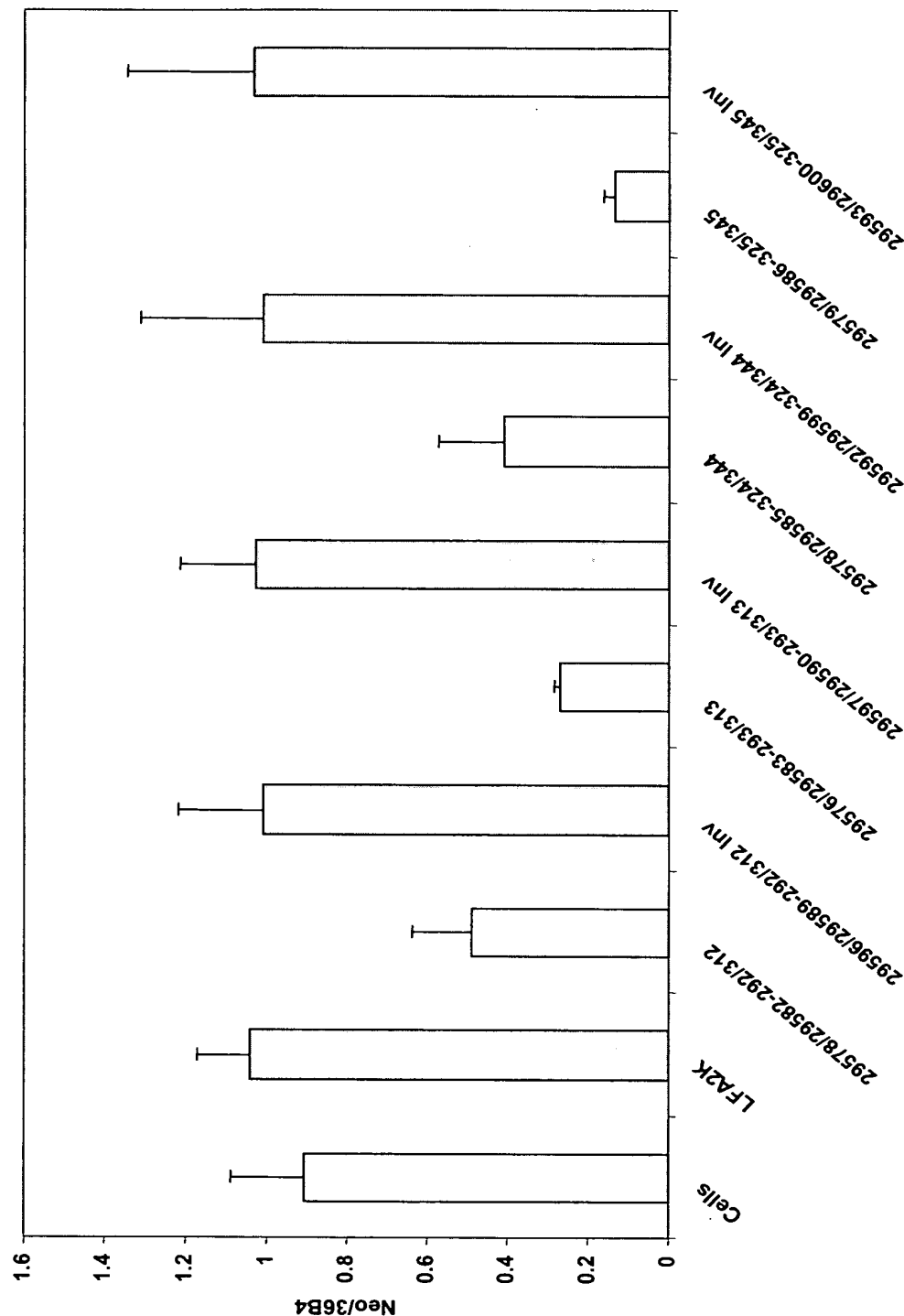
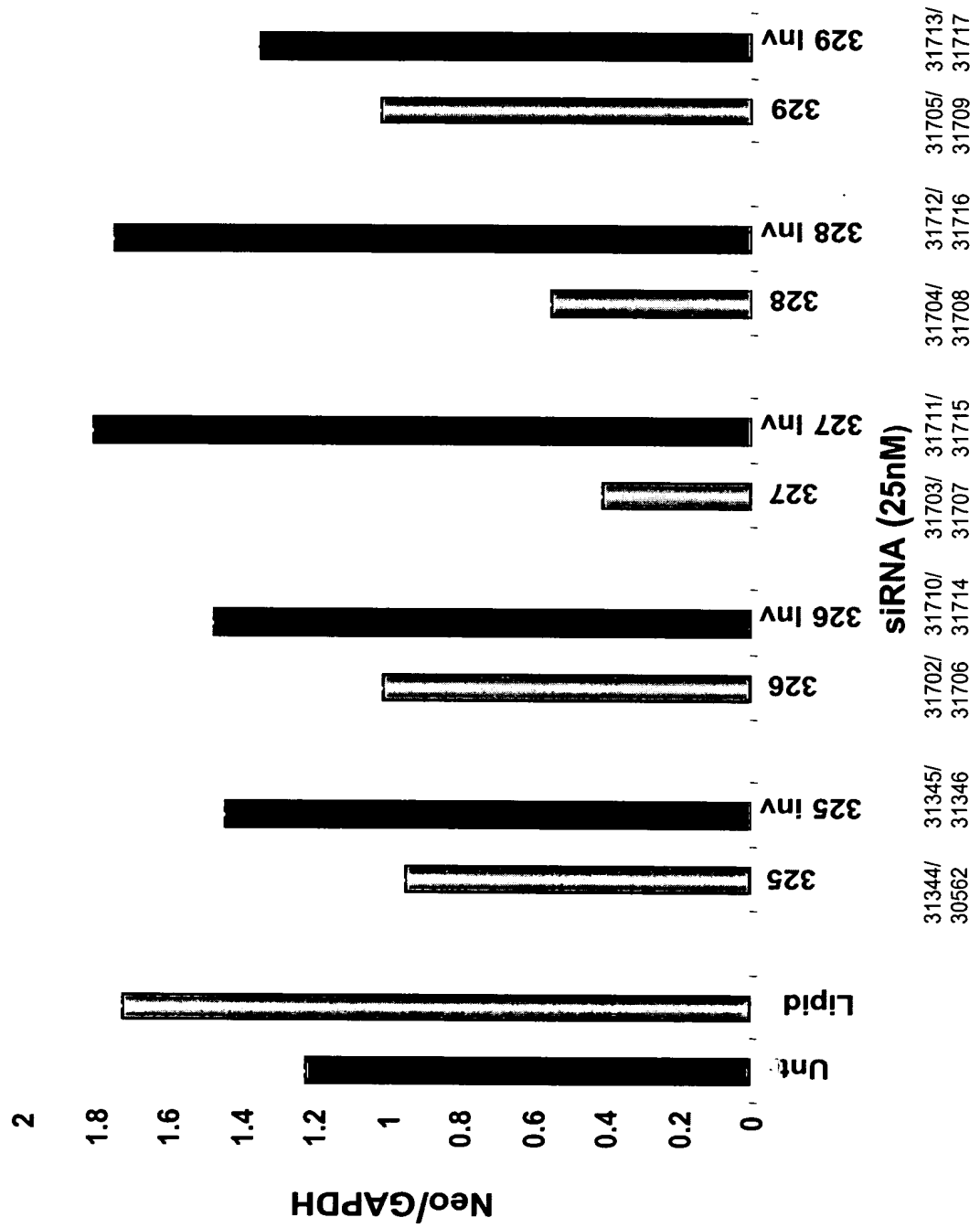


Figure 40: Activity of Stab 7/8 siNA Leads in HCV Subgenomic Replicon



**Figure 41: Dose Response with Fully Modified
HCV Site 327 siNA**

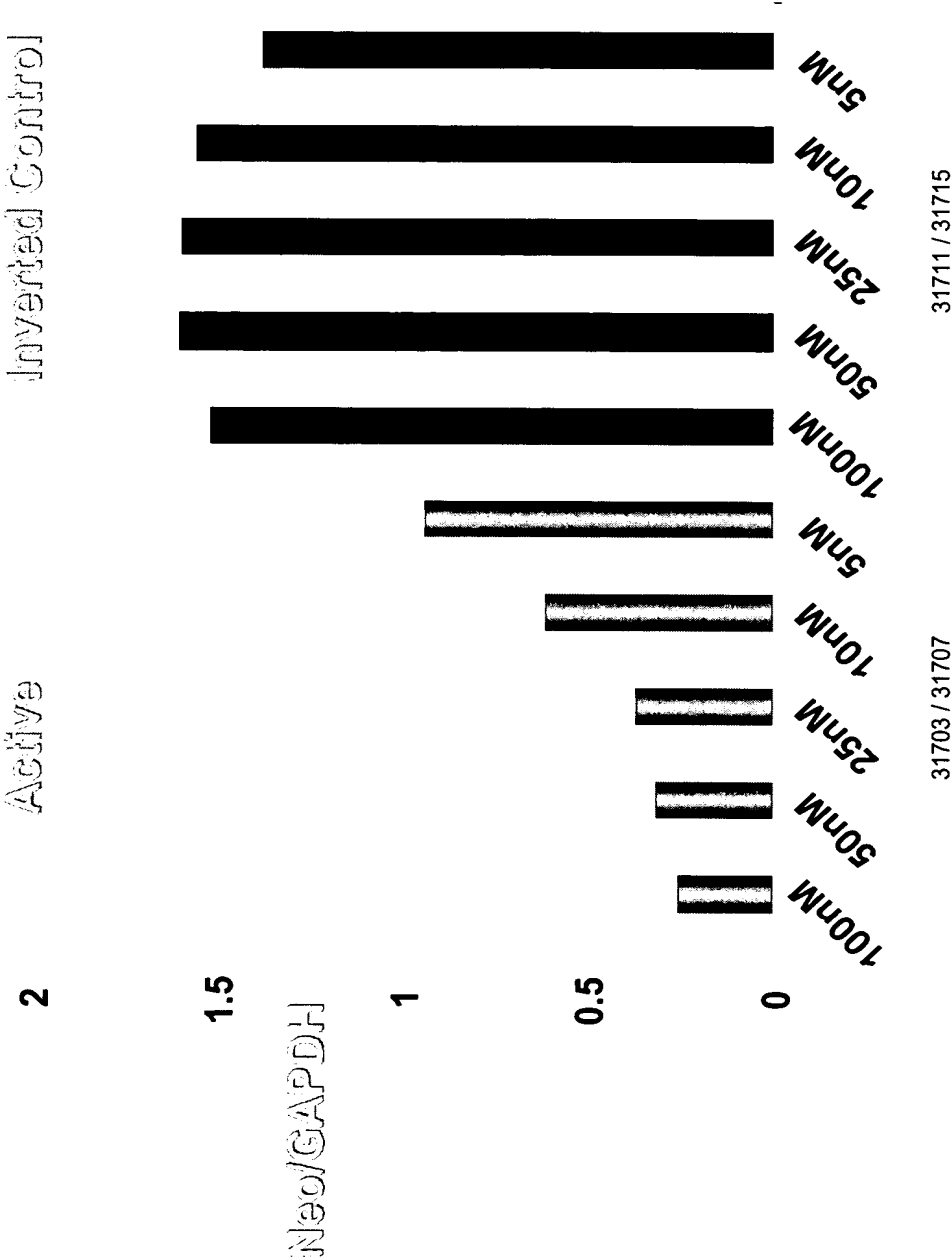


Figure 42: Solid Phase Post-synthetic conjugation of pterioic acid

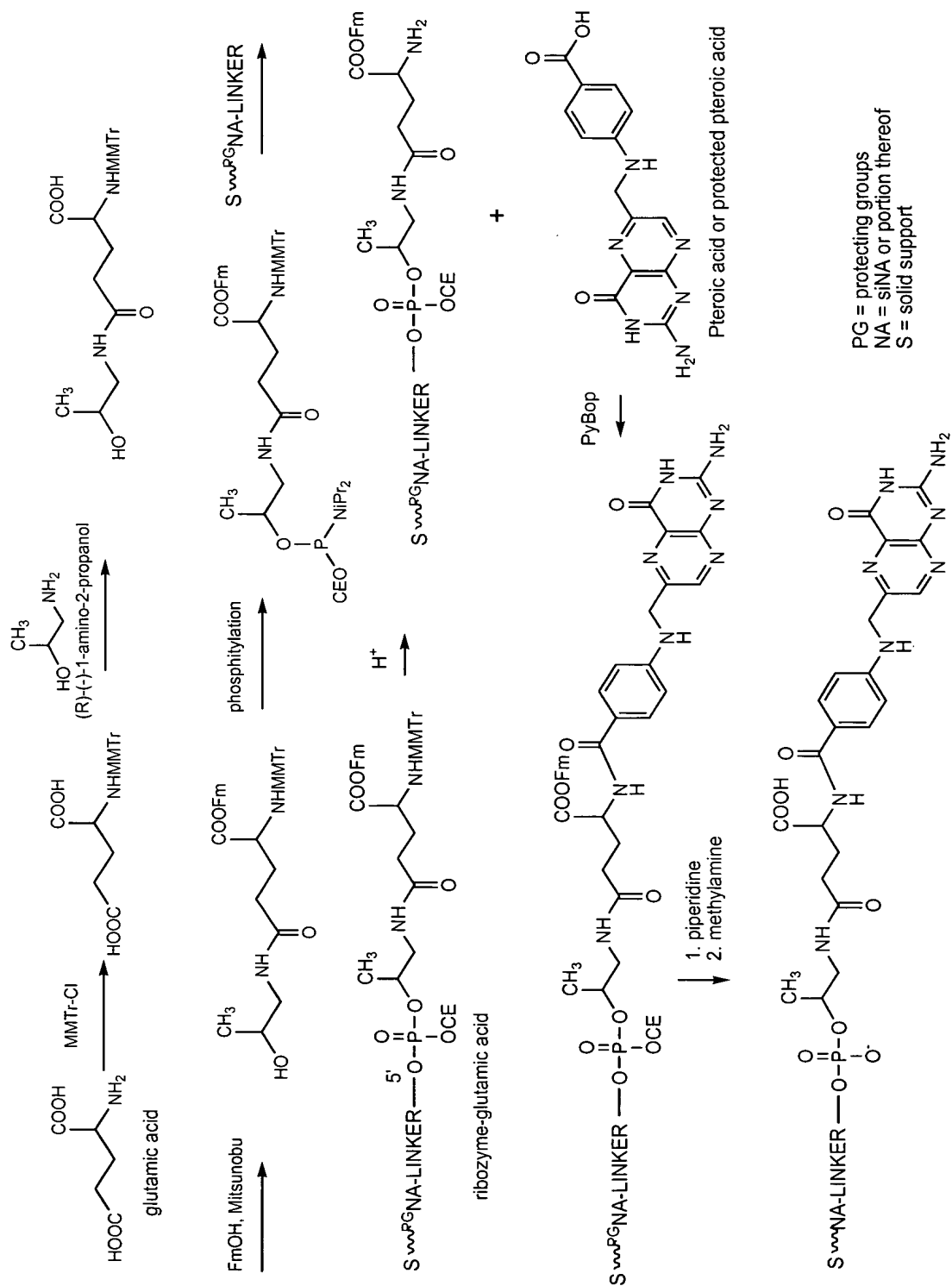
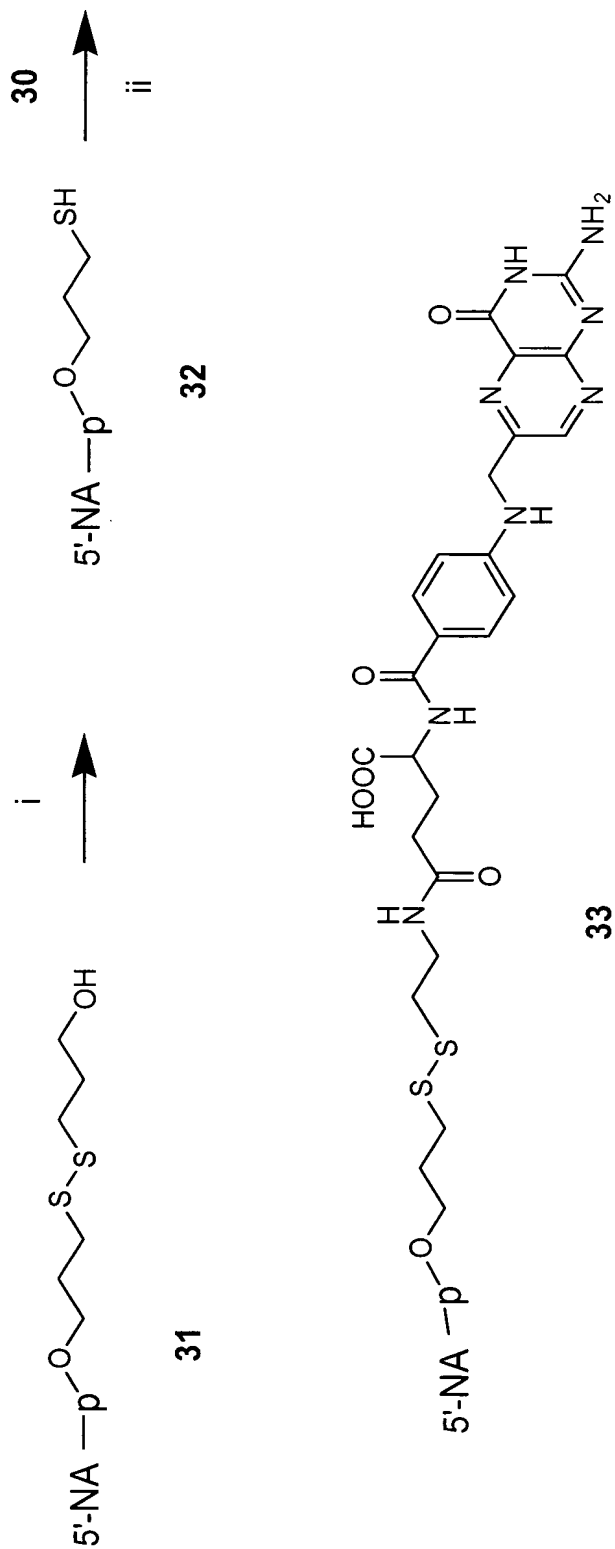
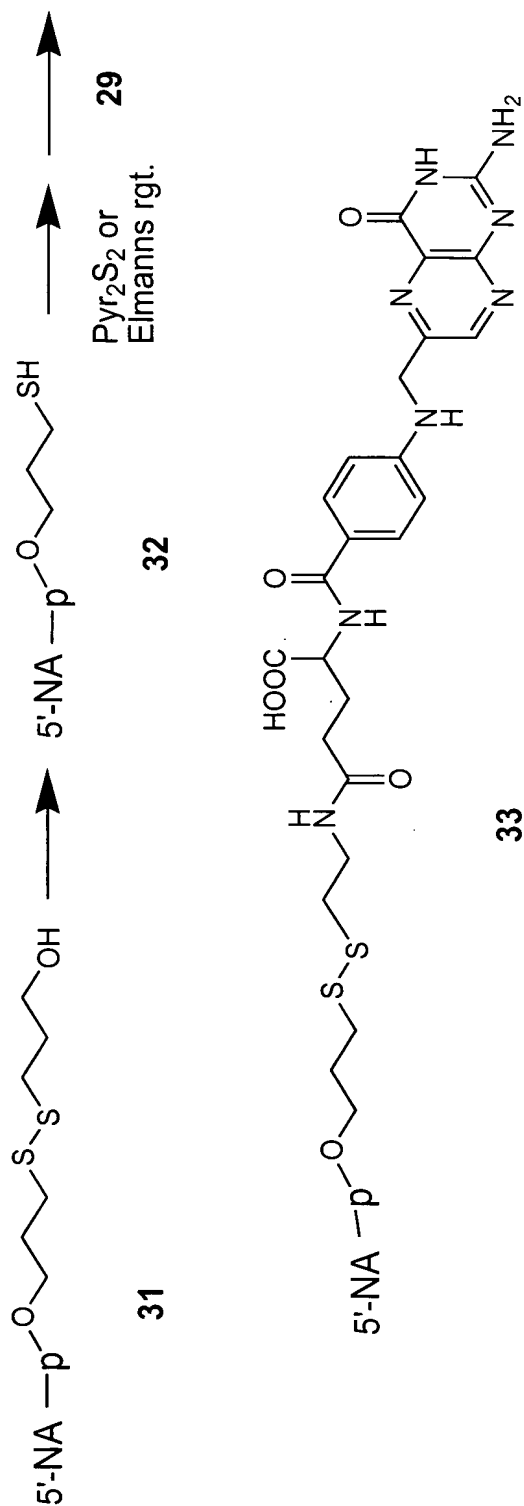


Figure 43



NA = siNA or a portion thereof
p = phosphorous moiety

Figure 44



NA = siNA or a portion thereof
 p = phosphorous moiety

Figure 45: Solid Phase Post-synthetic conjugation of pterioic acid

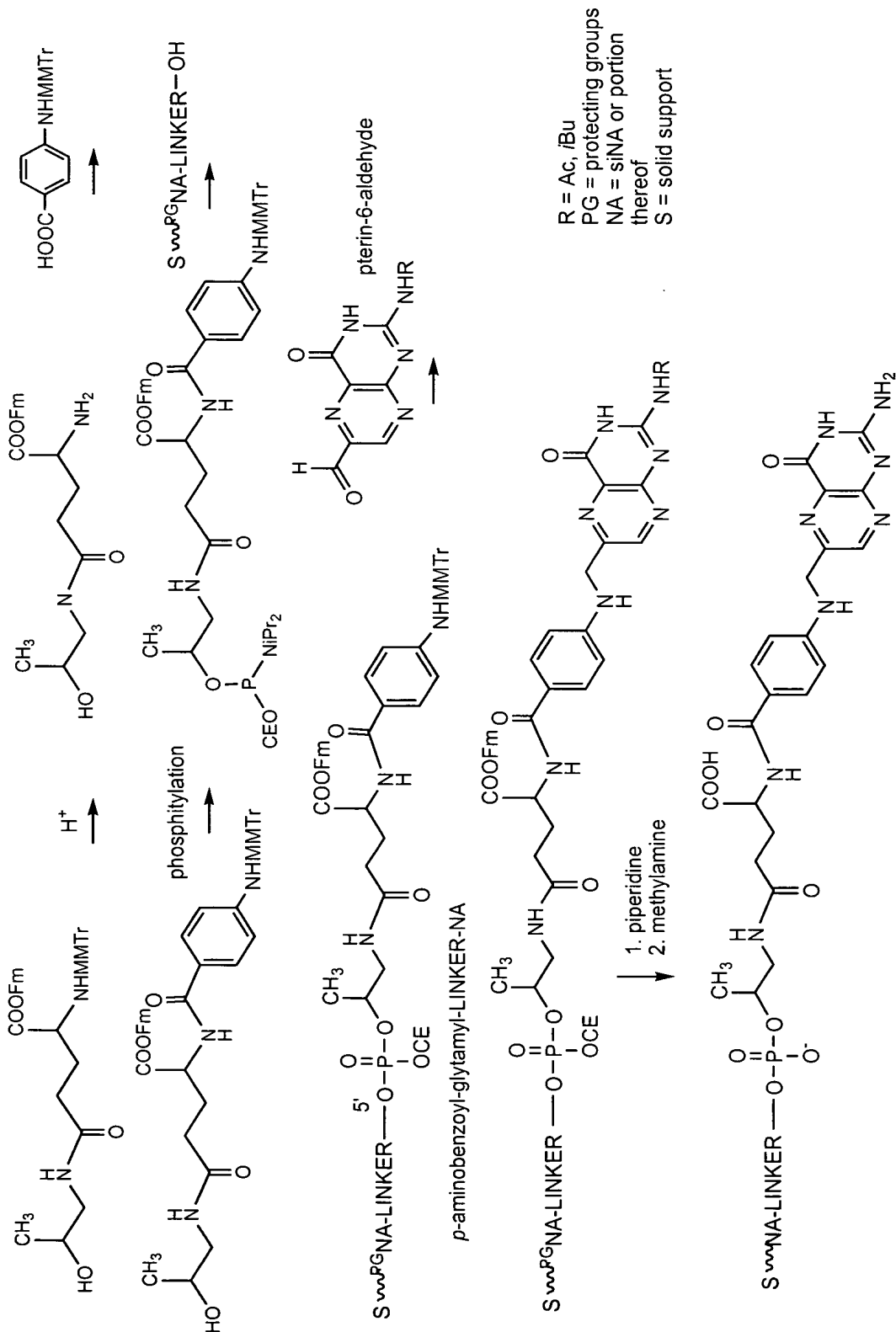


Figure 46: Synthesis of N-acetyl-D-galactosamine-2'-aminouridine

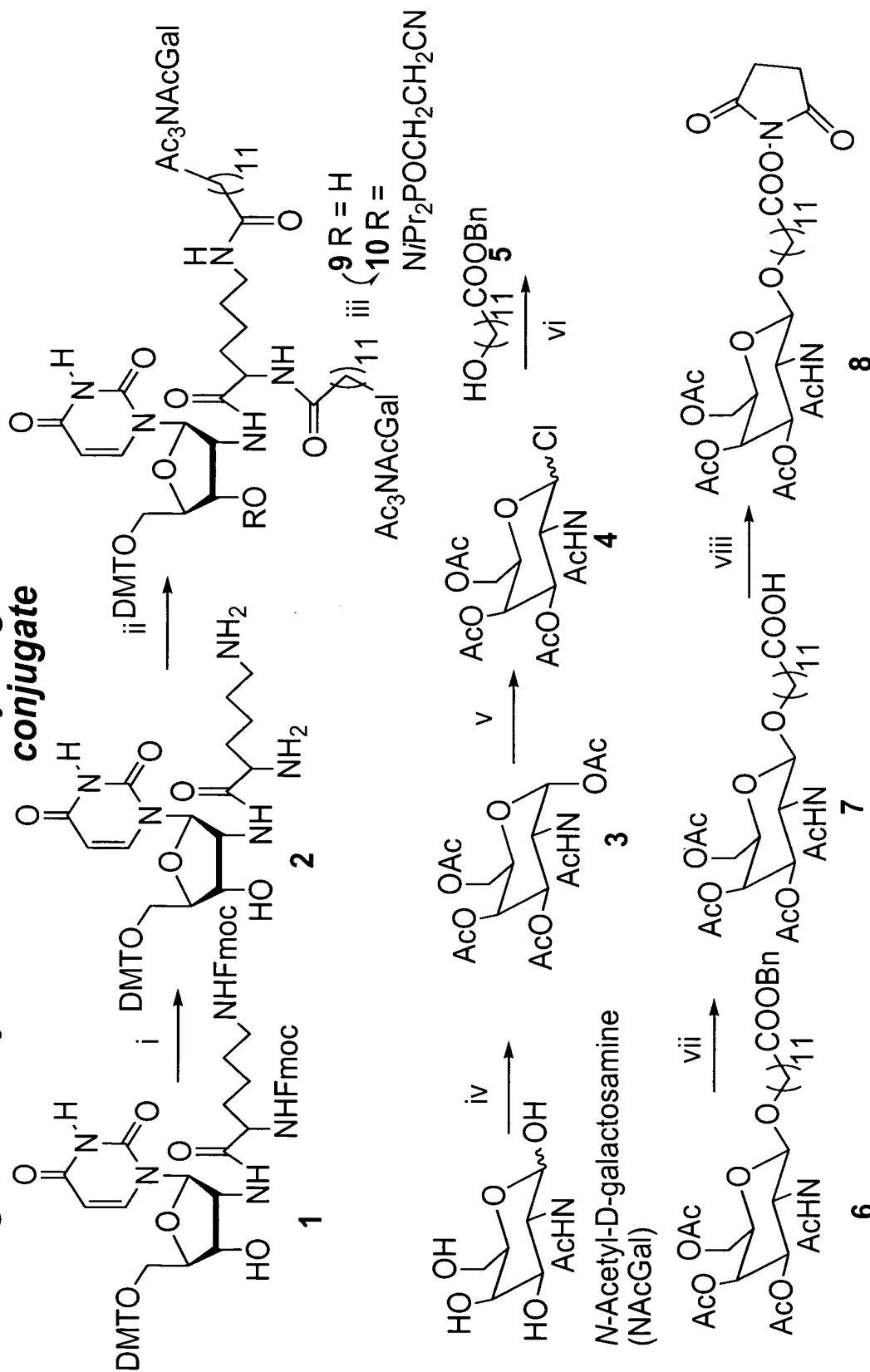
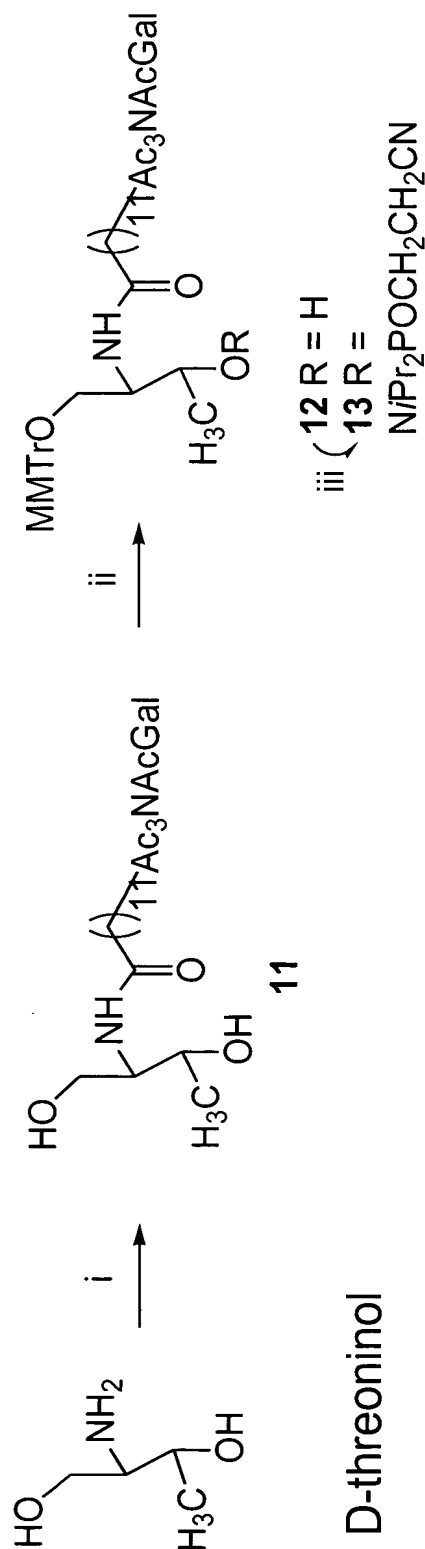
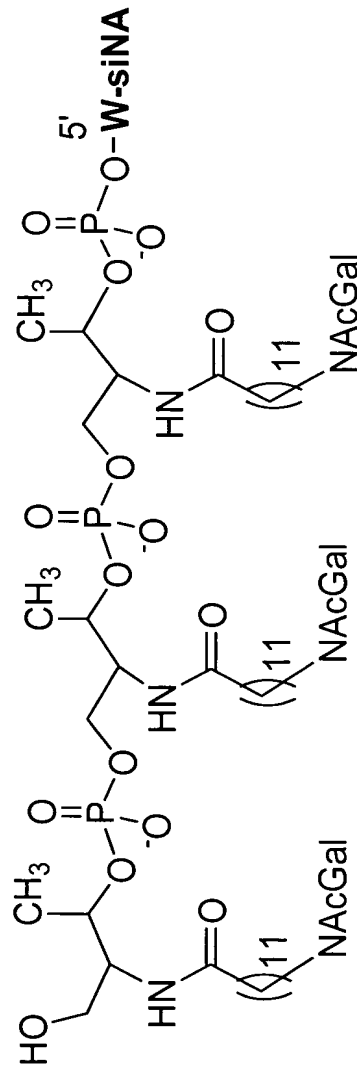


Figure 47: Synthesis of N-acetyl-D-galactosamine-D-threoninol conjugate



Reagents and Conditions: (i) 7, DCC, *N*-hydroxysuccinimide, (ii) MMTr-Cl, pyridine, (iii) 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite, 1-methylimidazole, DIPEA, CH_2Cl_2 .

Figure 48: Conjugation of targeting ligands to the 5'-end of a siNA molecule



N-acetyl-D-galactosamine conjugate

Figure 49: Synthesis of dodecanoic acid linker

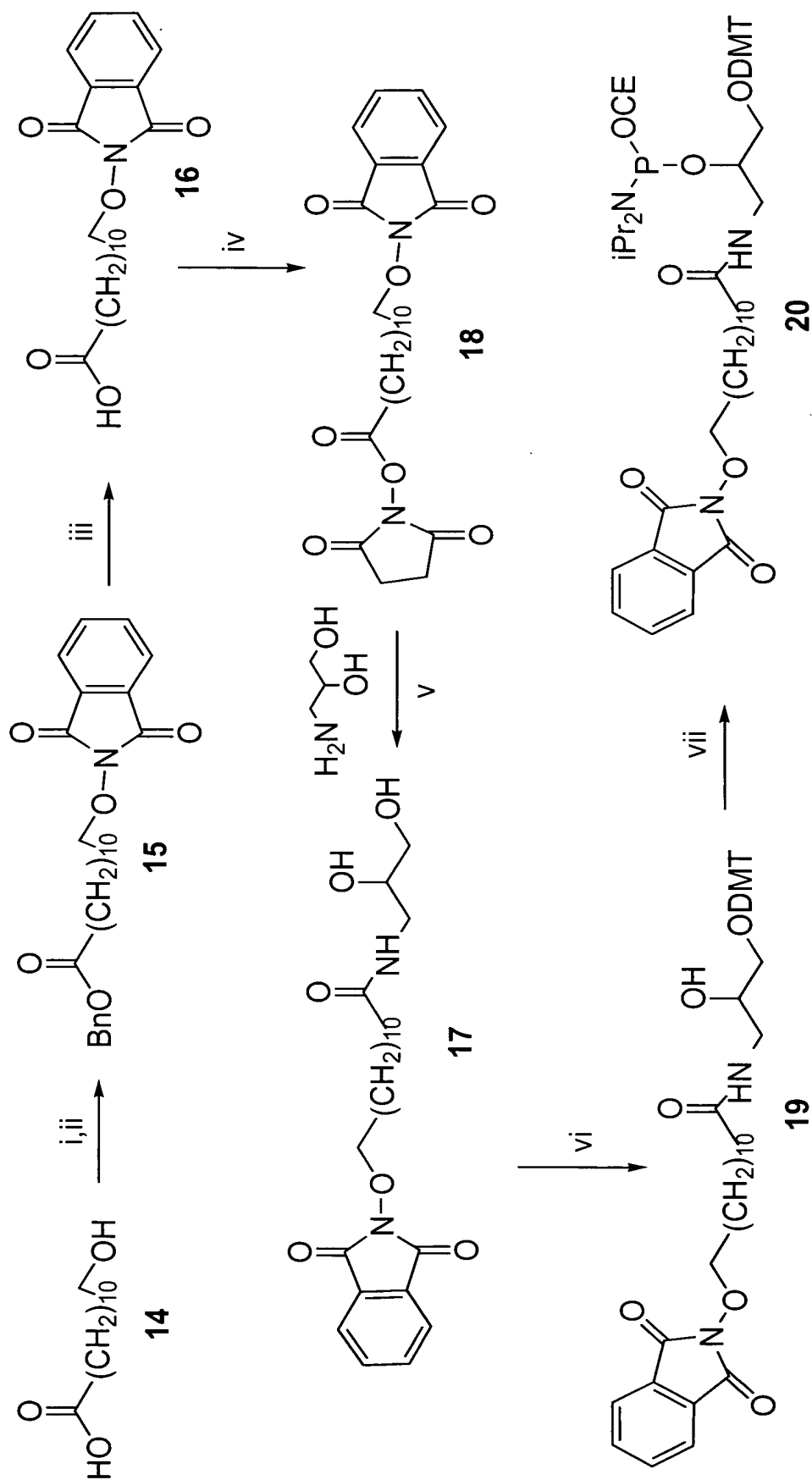


Figure 50: Oxime linked siNA/Peptide Conjugate

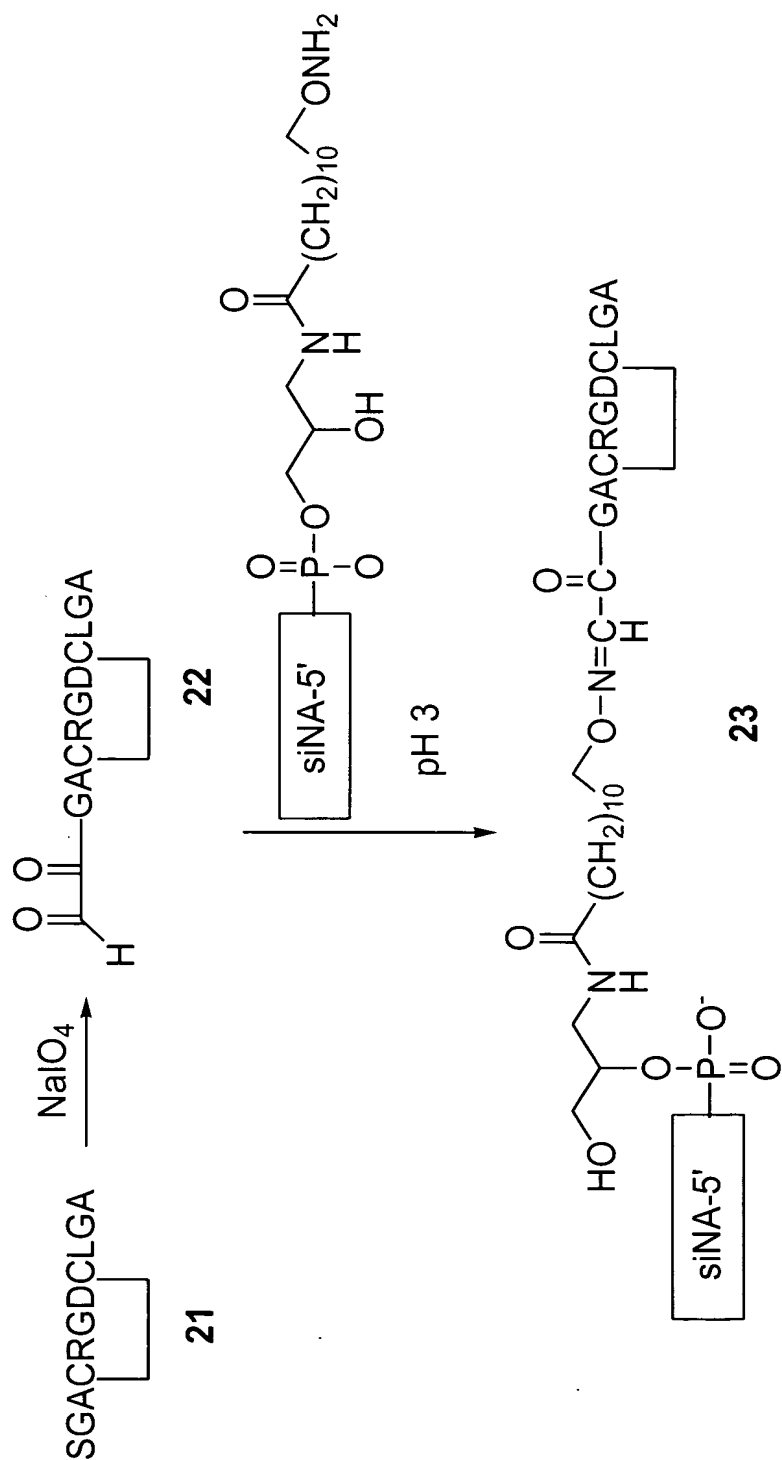
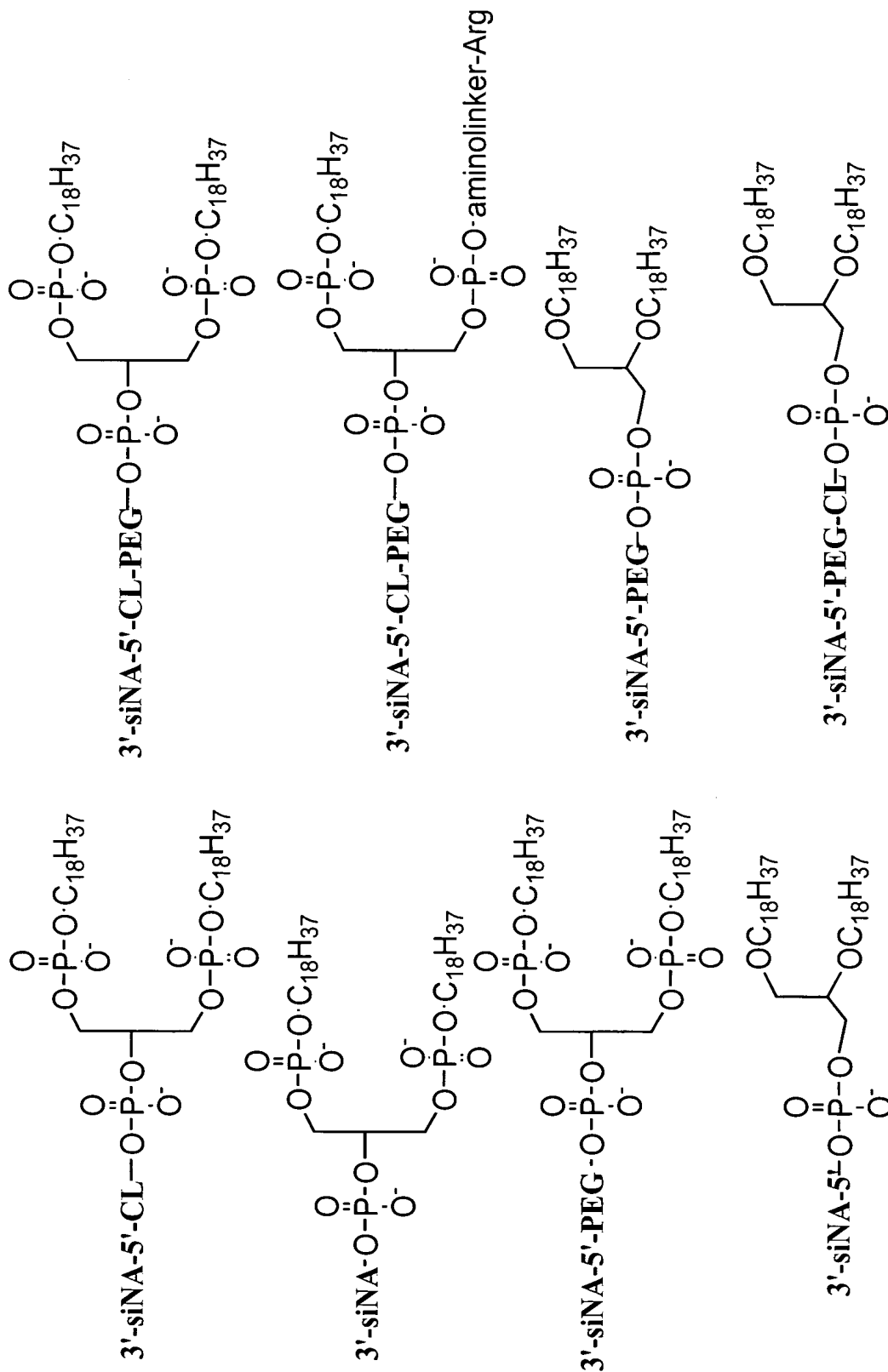


Figure 51: siNA/Phospholipid Conjugates



PEG=polyethylene glycol

CL=cleavable linker (e.g. A-dT, C-dT)

siNA= short interfering nucleic acid molecule or a portion thereof

Figure 52: siNA Phospholipid Conjugate

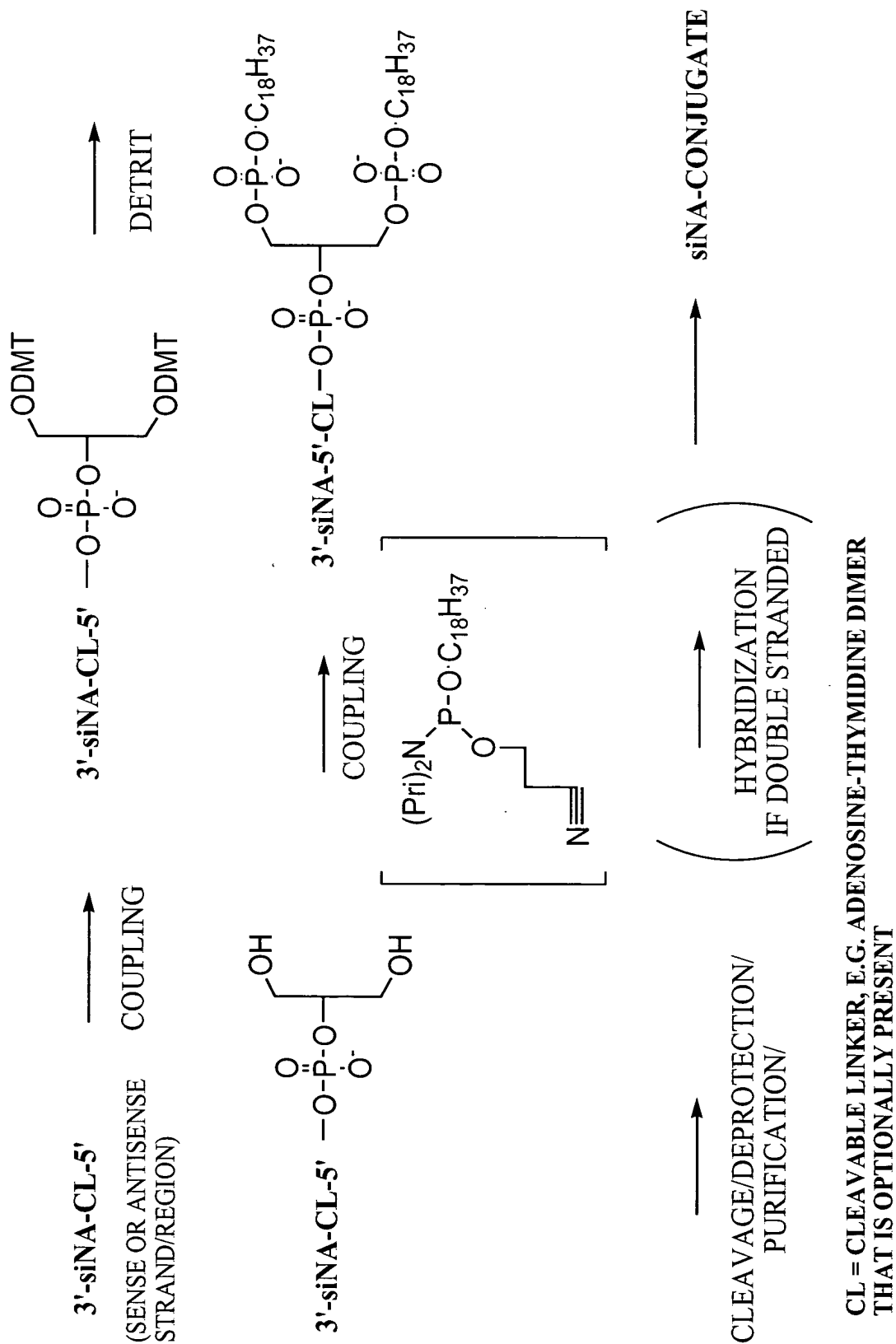
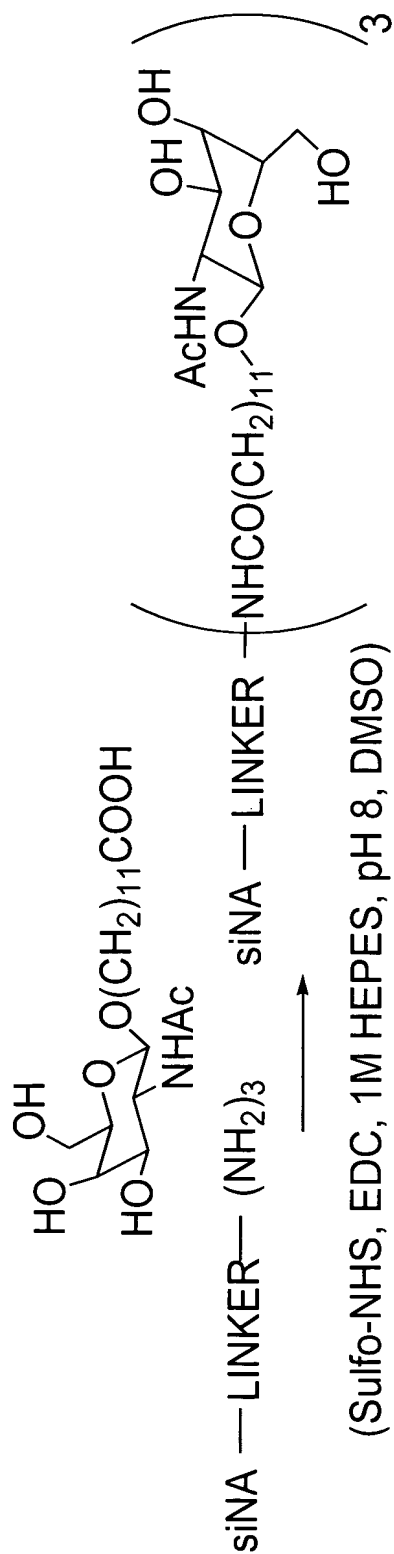
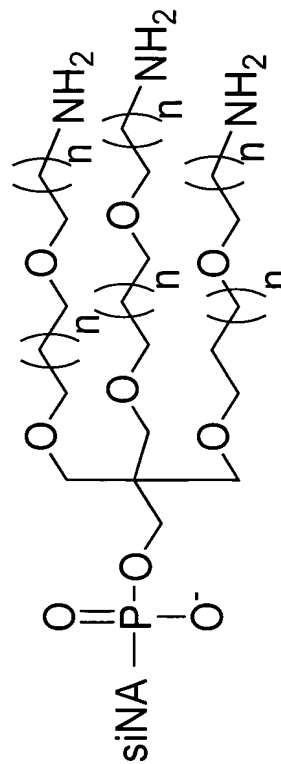


Figure 53: siNA-NAcGalactosamine post-synthetic coupling



FOR EXAMPLE: OLIGO-LINKER =



Where n is an integer from 1 to 20

Figure 54: siNA Cholesterol Conjugate

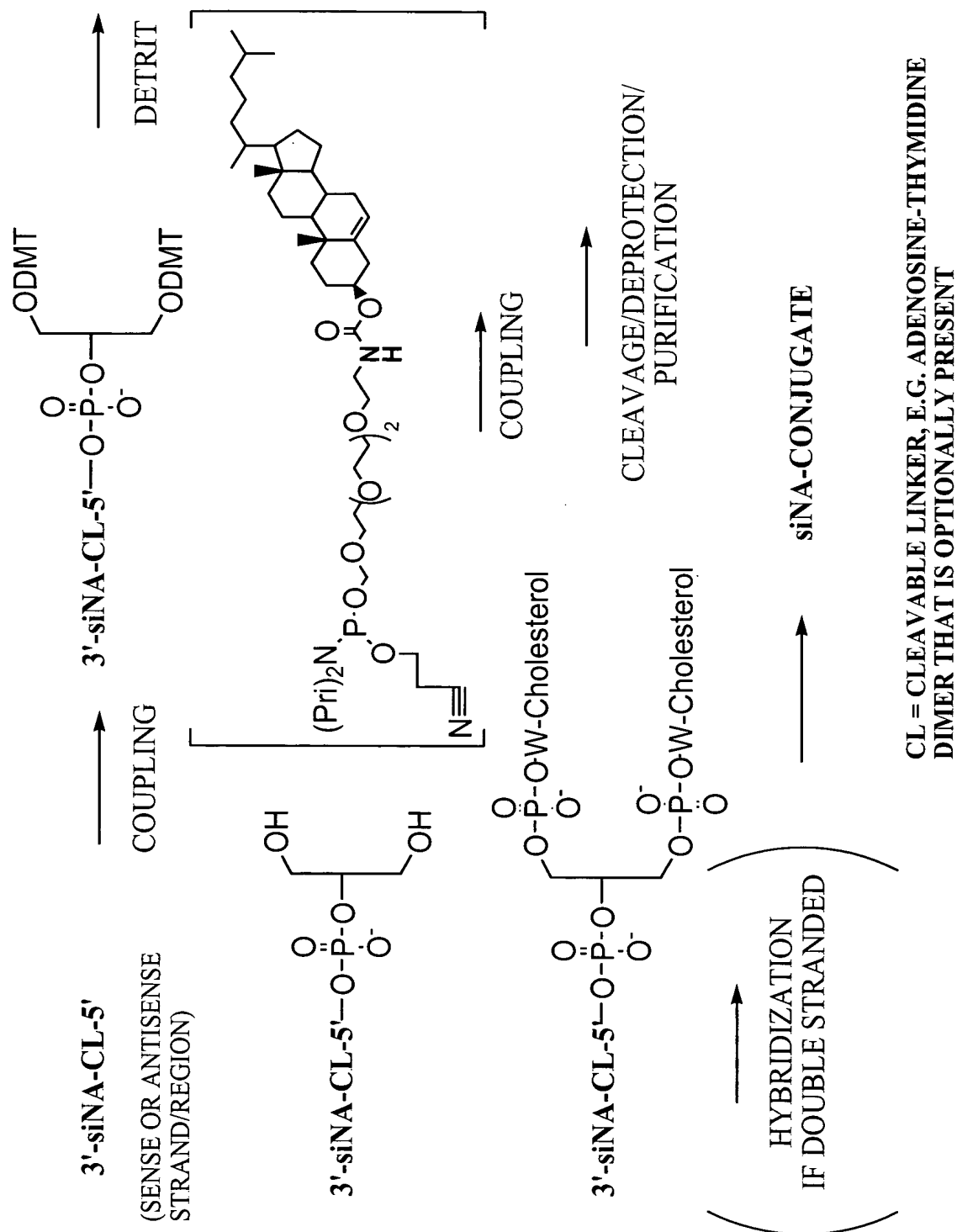
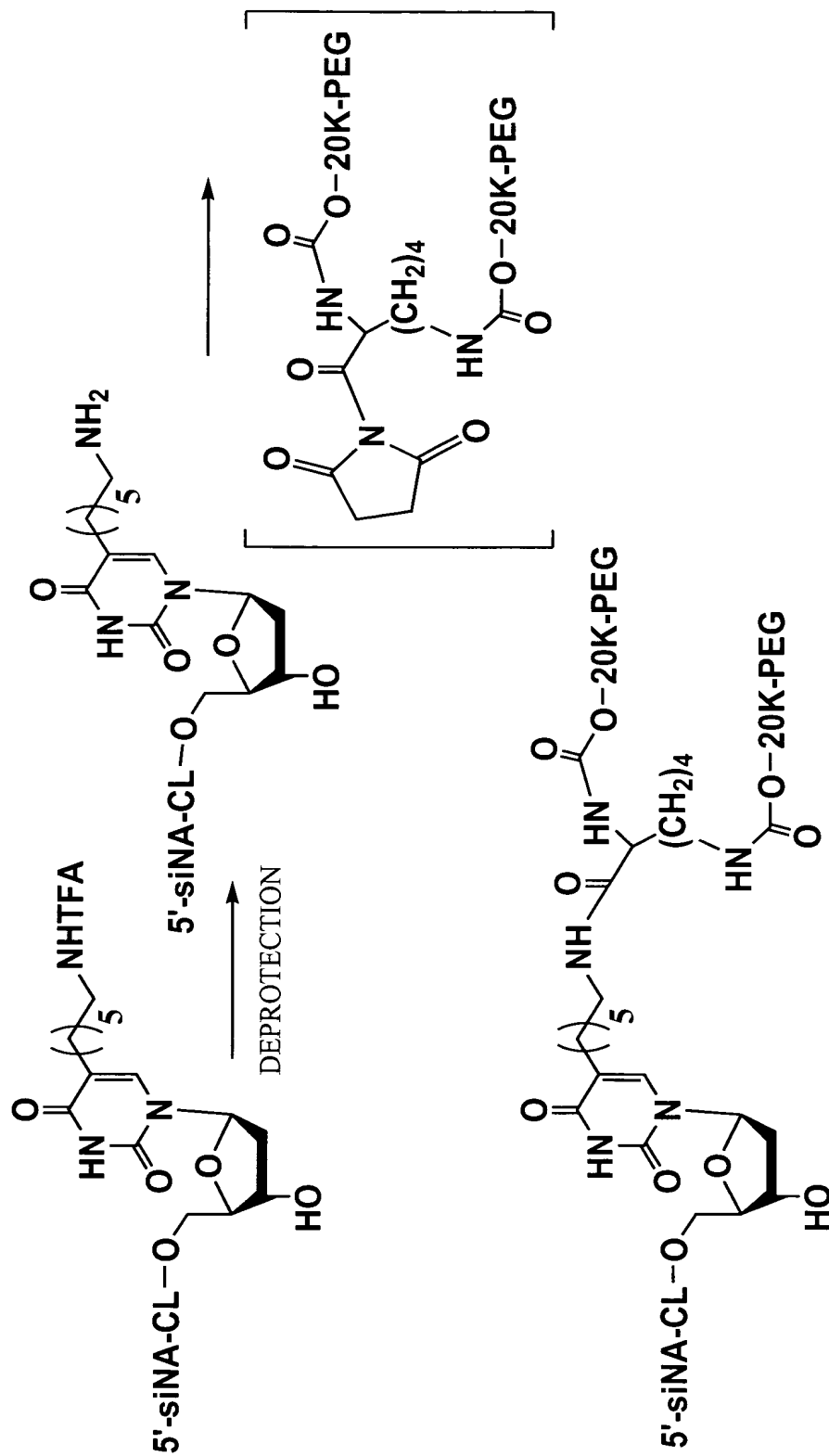
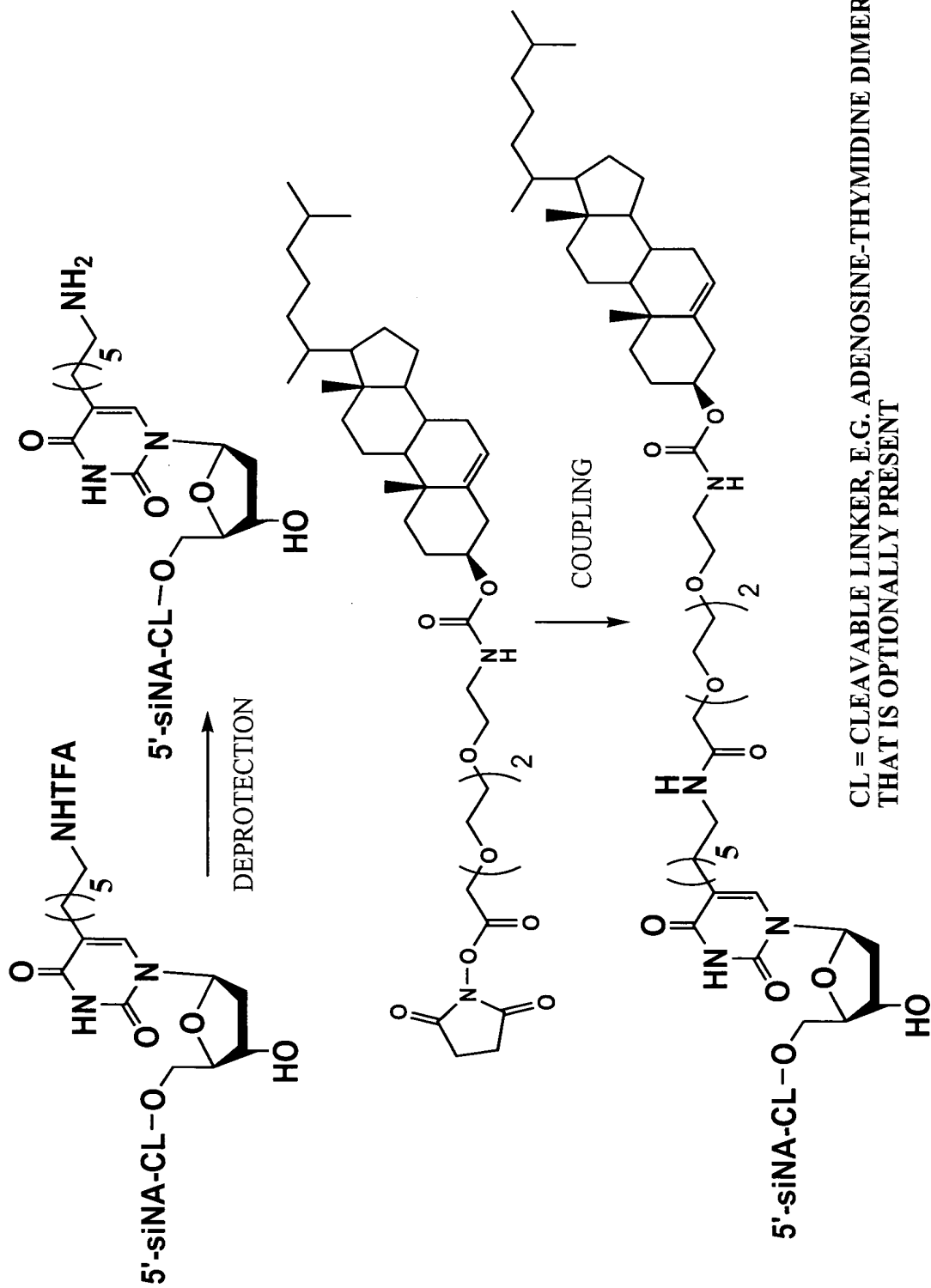


Figure 55: siNA 3'-PEG Conjugate



CL = CLEAVABLE LINKER, E.G. ADENOSINE-THYMIDINE DIMER THAT IS OPTIONALLY PRESENT

Figure 56: siNA 3'-Cholesterol Conjugate



Chemical structures of various siRNA derivatives are shown, including:

- 3'-siNA-5'-CL
- 3'-siNA
- 3'-siNA-5'-PEG
- 3'-siNA-5'
- 3'-siNA-5'-CL-PEG
- 3'-siNA-5'-CL-PEG-O-aminolinker-Arg
- 3'-siNA-5'-PEG-O-W-CHOL
- 3'-siNA-5'-PEG-CL-O-W-CHOL

PEG=polyethylene glycol

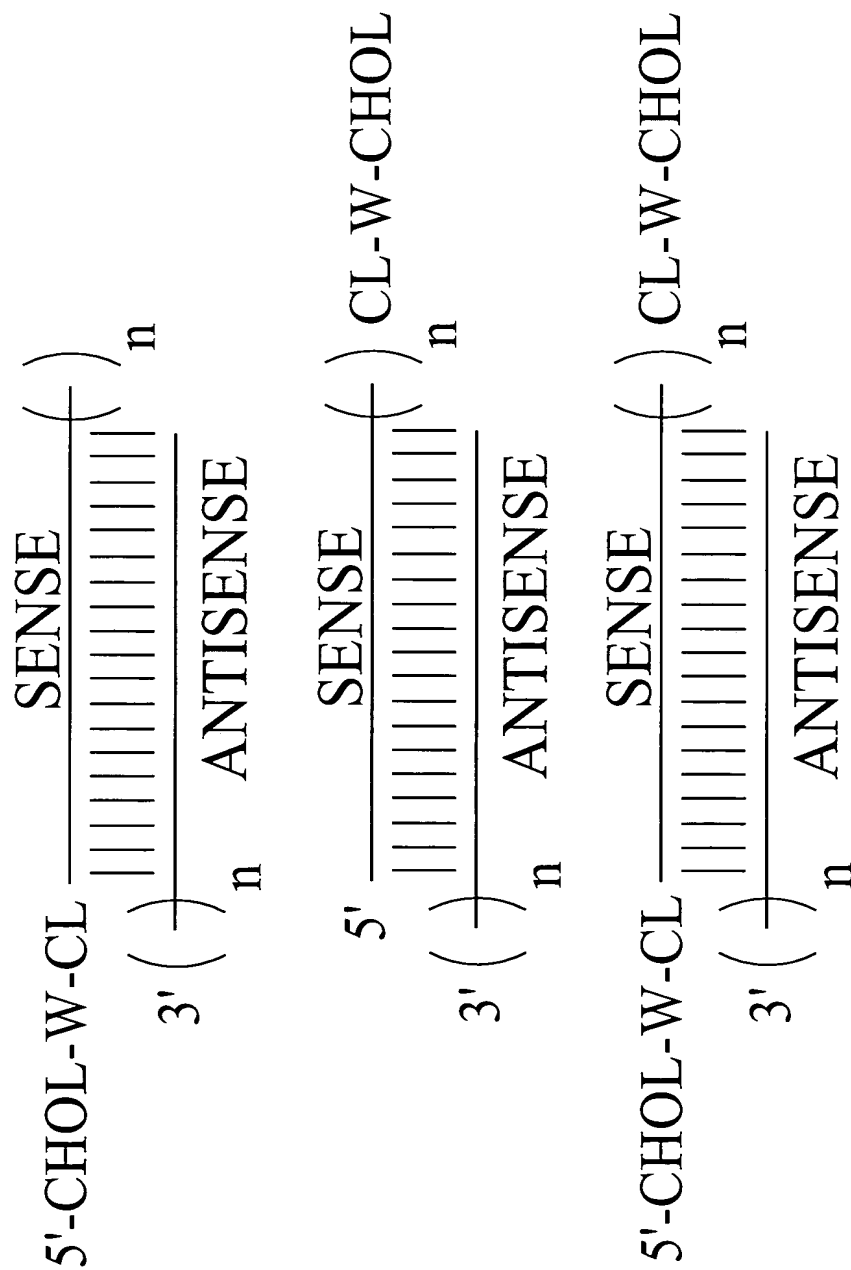
CL=cleavable linker (e.g. A-dT, C-dT)

siNA= short interfering nucleic acid molecule or a portion thereof

CHOL=cholesterol or an analog or metabolite thereof

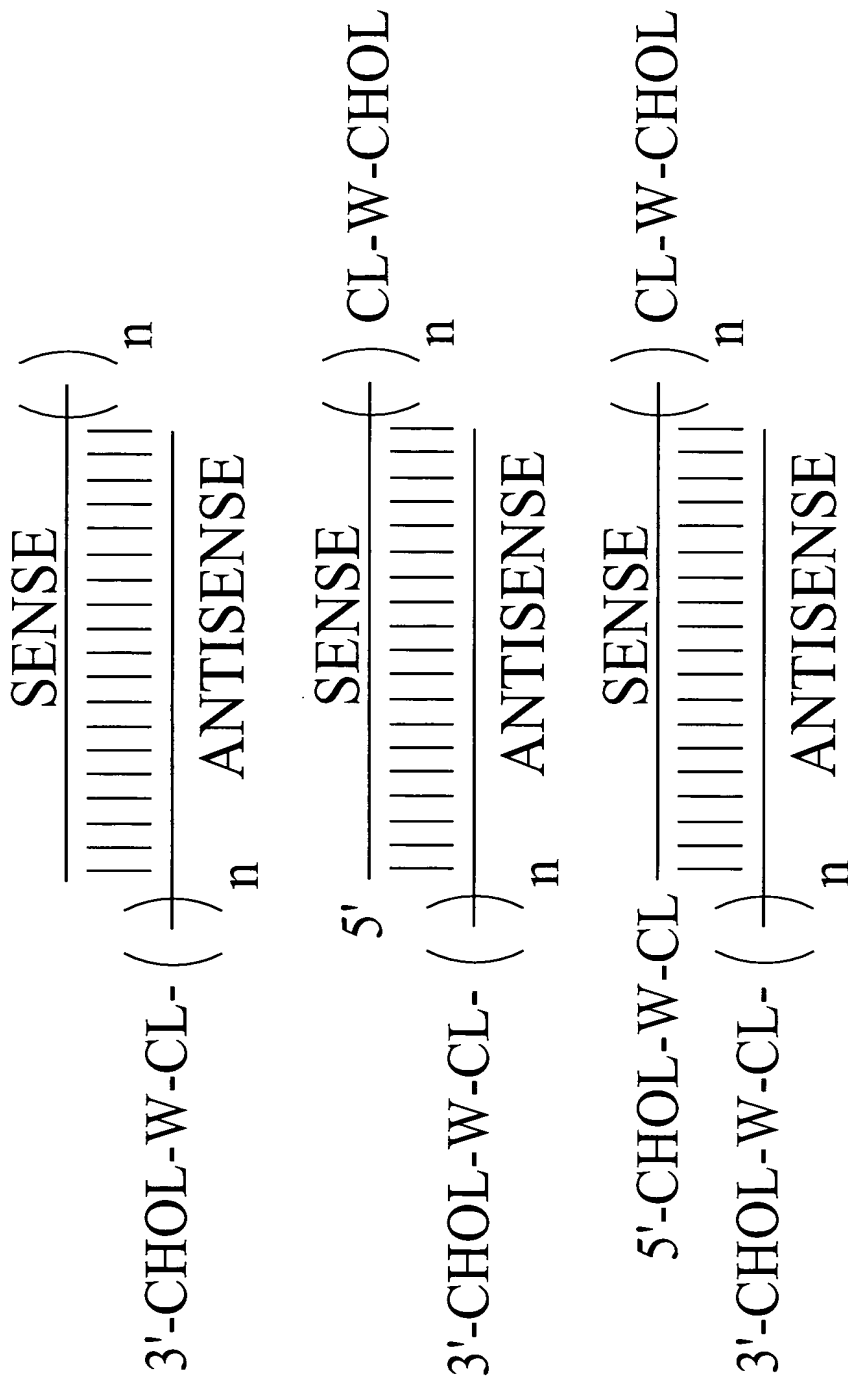
W= linker molecule (see for example Formulae 109 or 112)

Figure 58: siNA Cholesterol Conjugates



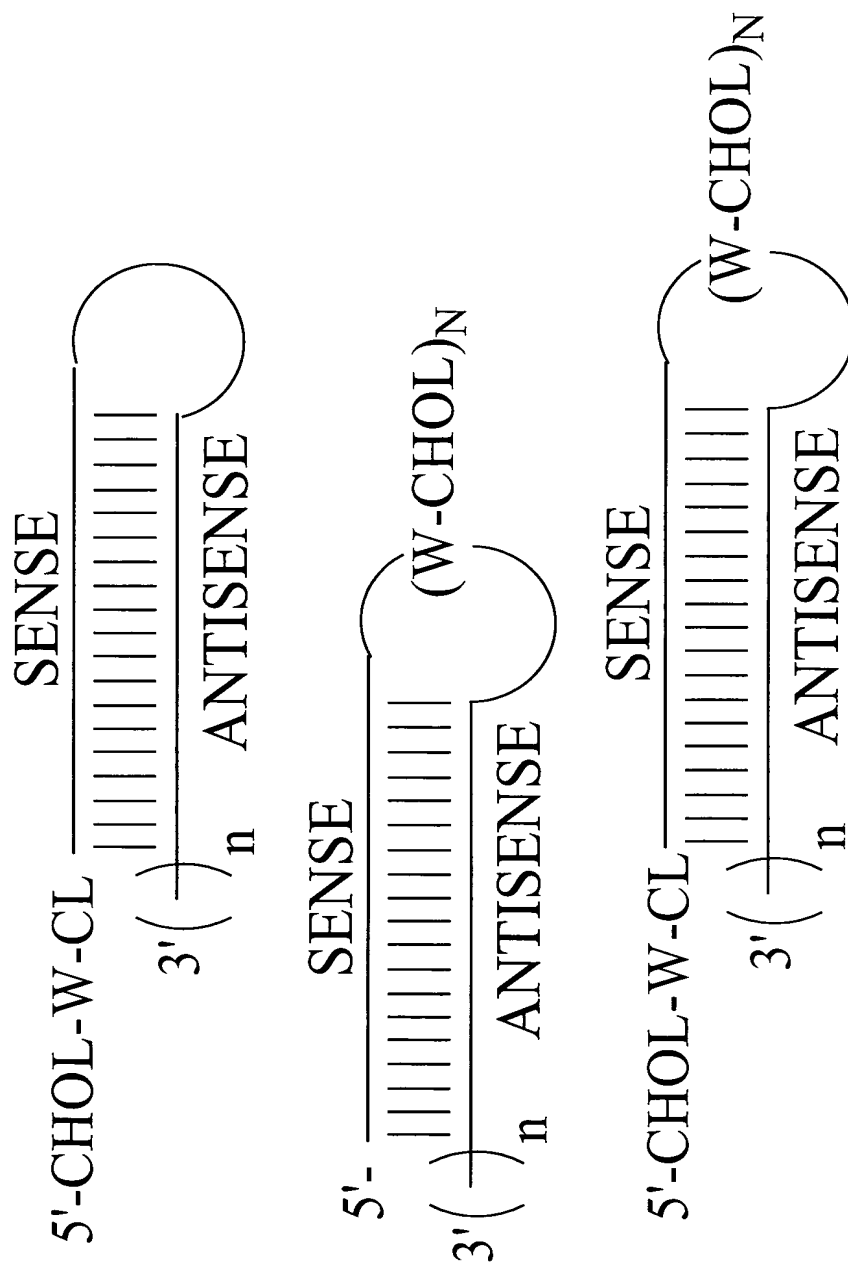
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
 CHOL=cholesterol or an analog or metabolite thereof
 W= linker molecule (see for example Formulae 107, 108, 109 or 115)
 n = integer, e.g. 1, 2, or 3

Figure 59: siNA Cholesterol Conjugates



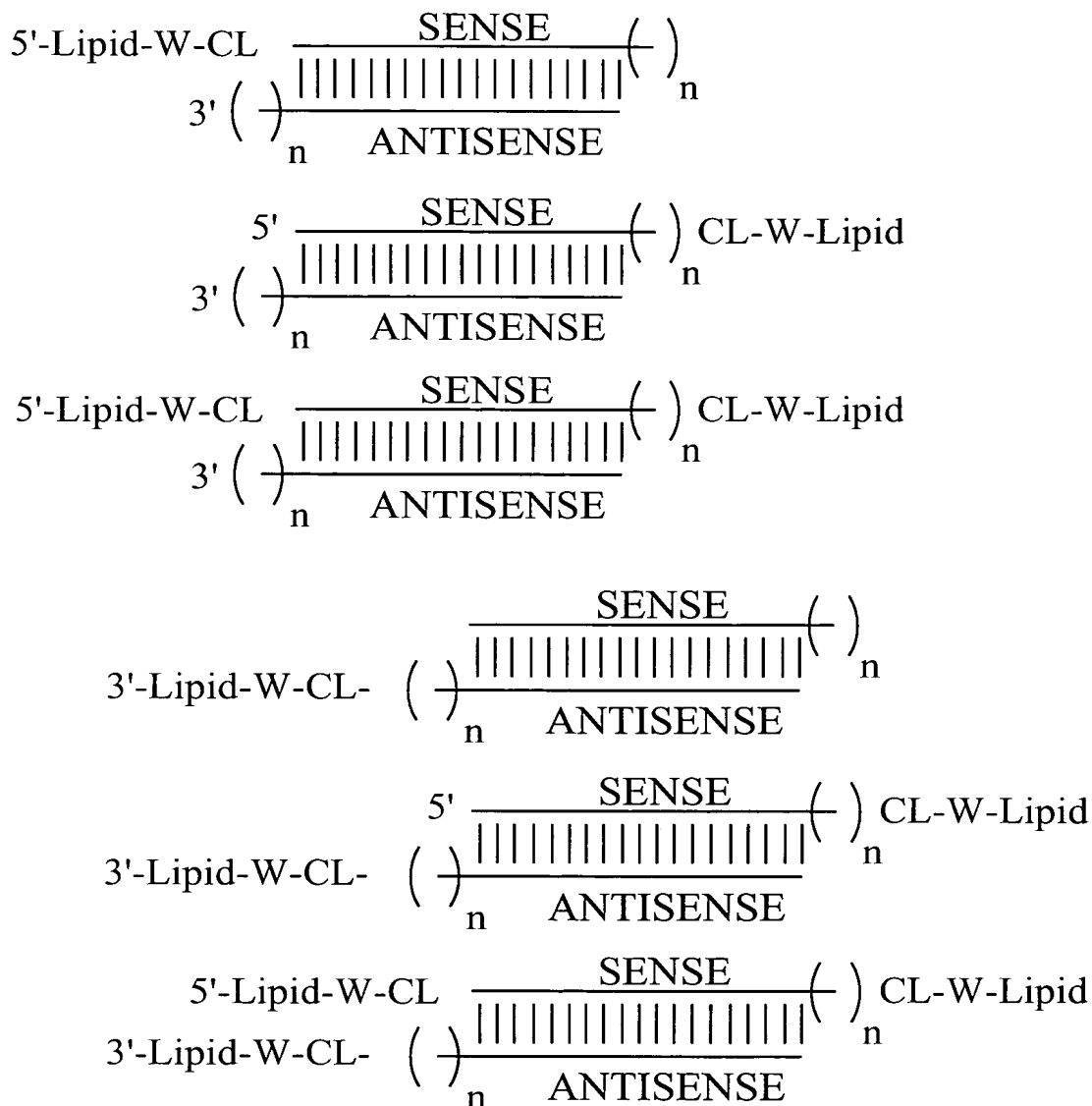
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
 CHOL=cholesterol or an analog or metabolite thereof
 W= linker molecule (see for example Formulae 107, 108, 109 or 110)
 n = integer, e.g. 1, 2, or 3

Figure 60: siNA Cholesterol Conjugates



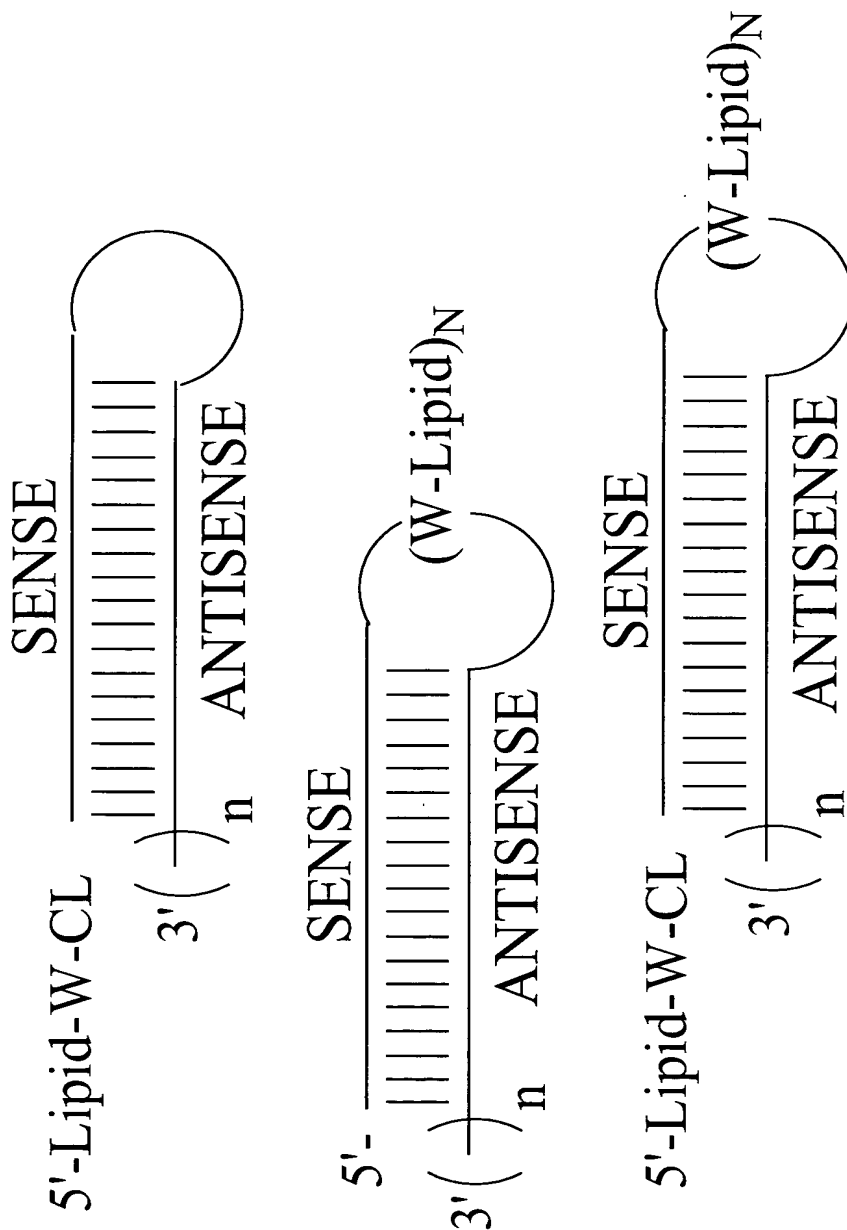
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
 CHOL=cholesterol or an analog or metabolite thereof
 W= linker molecule (see for example Formulae 107, 108, 109 or 112)
 n = integer, e.g. 1, 2, or 3
 N=integer, e.g. 1, 2, 3, or 4

Figure 61: siNA Lipid Conjugates



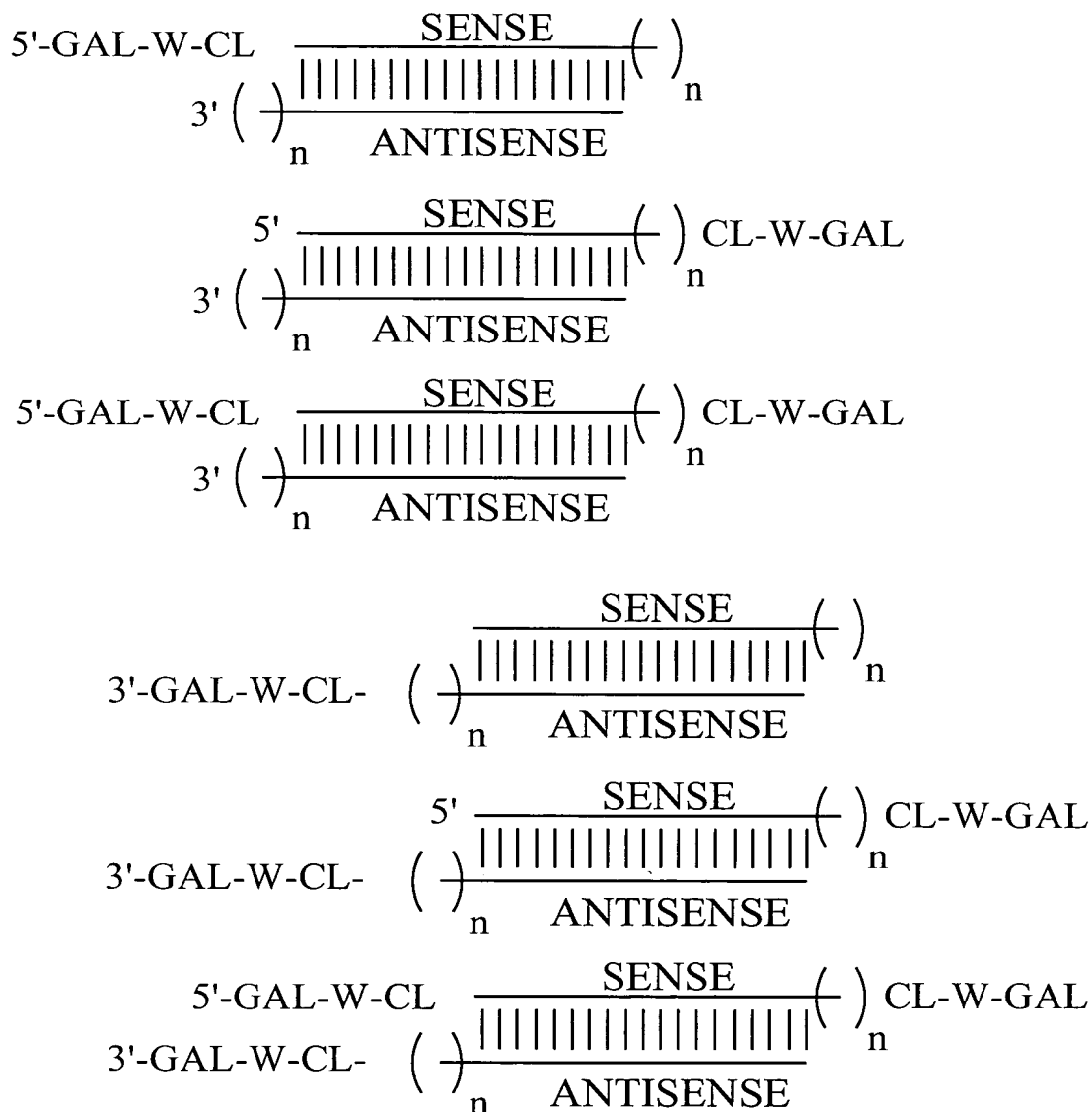
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
Lipid=Straight chain or branched alkyl or fatty acid, e.g. C₁₈H₃₇
W= linker molecule (see for example Formulae 48, 49, 64, or 65)
n = integer, e.g. 1, 2, or 3

Figure 62: siNA Lipid Conjugates



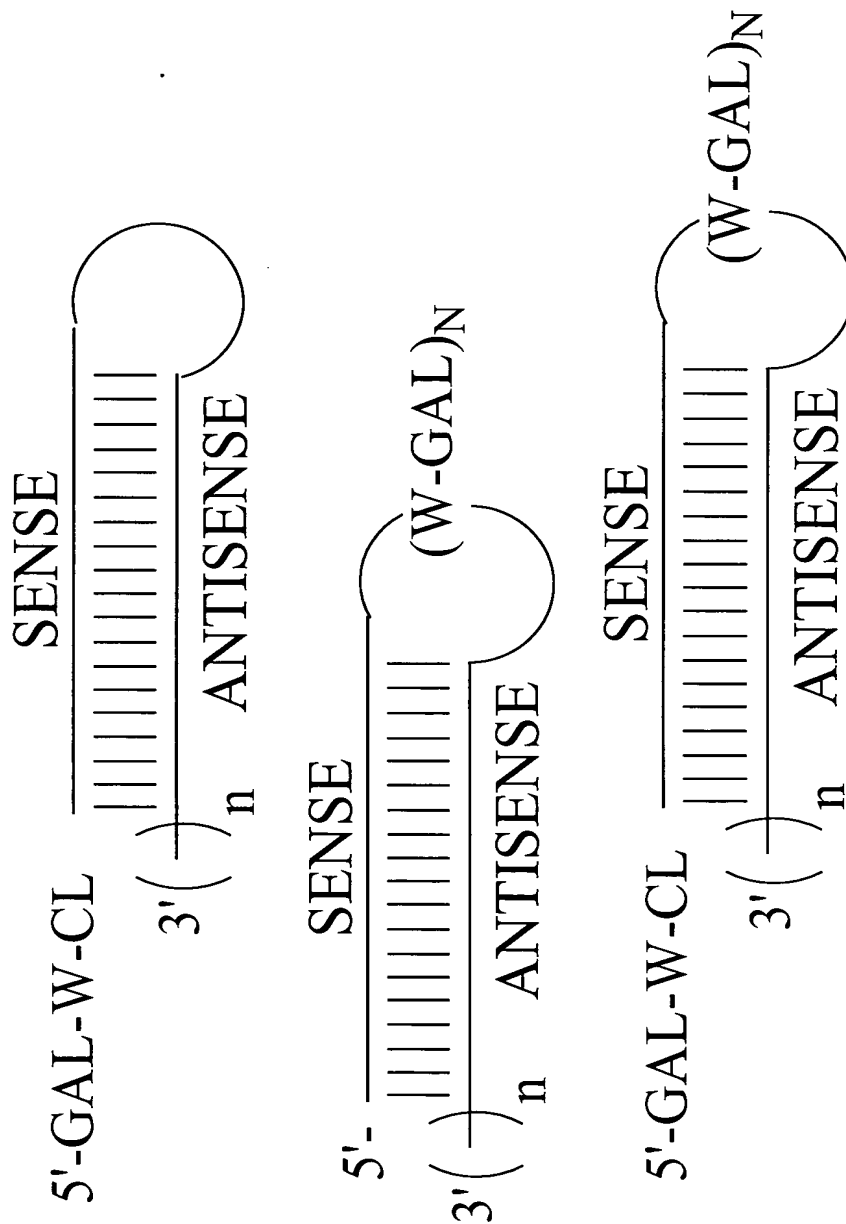
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
 Lipid=Straight chain or branched alkyl or fatty acid, e.g. C₁₈H₃₇
 W= linker molecule (see for example Formulae 48, 49, 64, or 65)
 n = integer, e.g. 1, 2, or 3
 N=integer, e.g. 1, 2, 3, or 4

Figure 63: siNA Galactosamine Conjugates



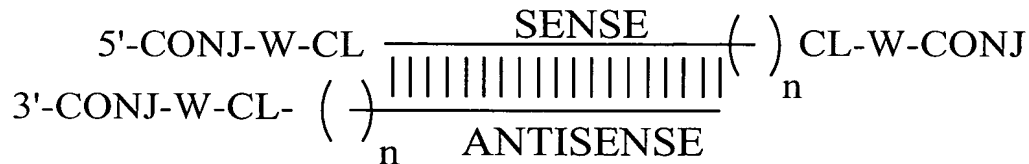
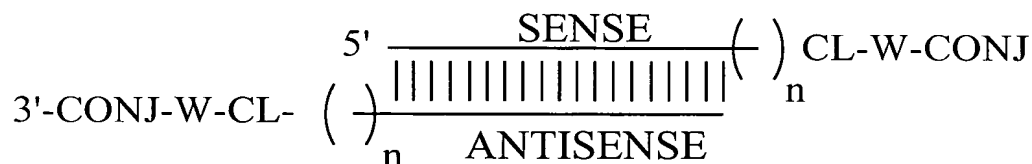
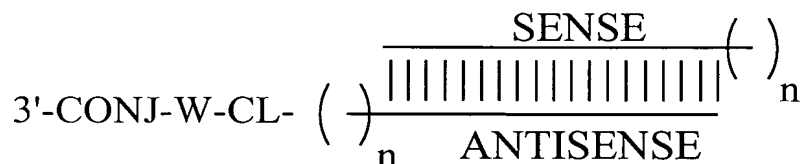
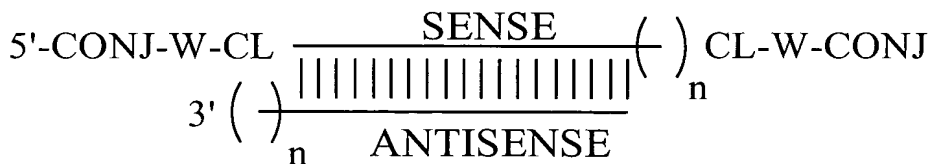
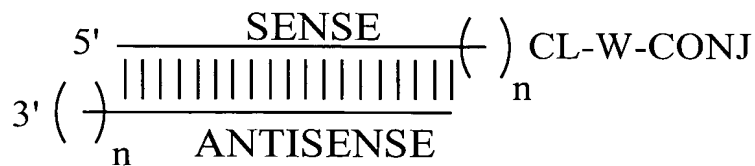
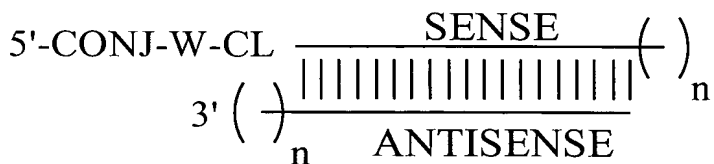
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
 GAL=GALACTOSAMINE; e.g. compounds having Formulae 51-56, 86, 92, 99, 100, 103, 105, 106
 W= linker molecule (see for example Formulae 102 or 103)
 n = integer, e.g. 1, 2, or 3

Figure 64: siNA Galactosamine Conjugates



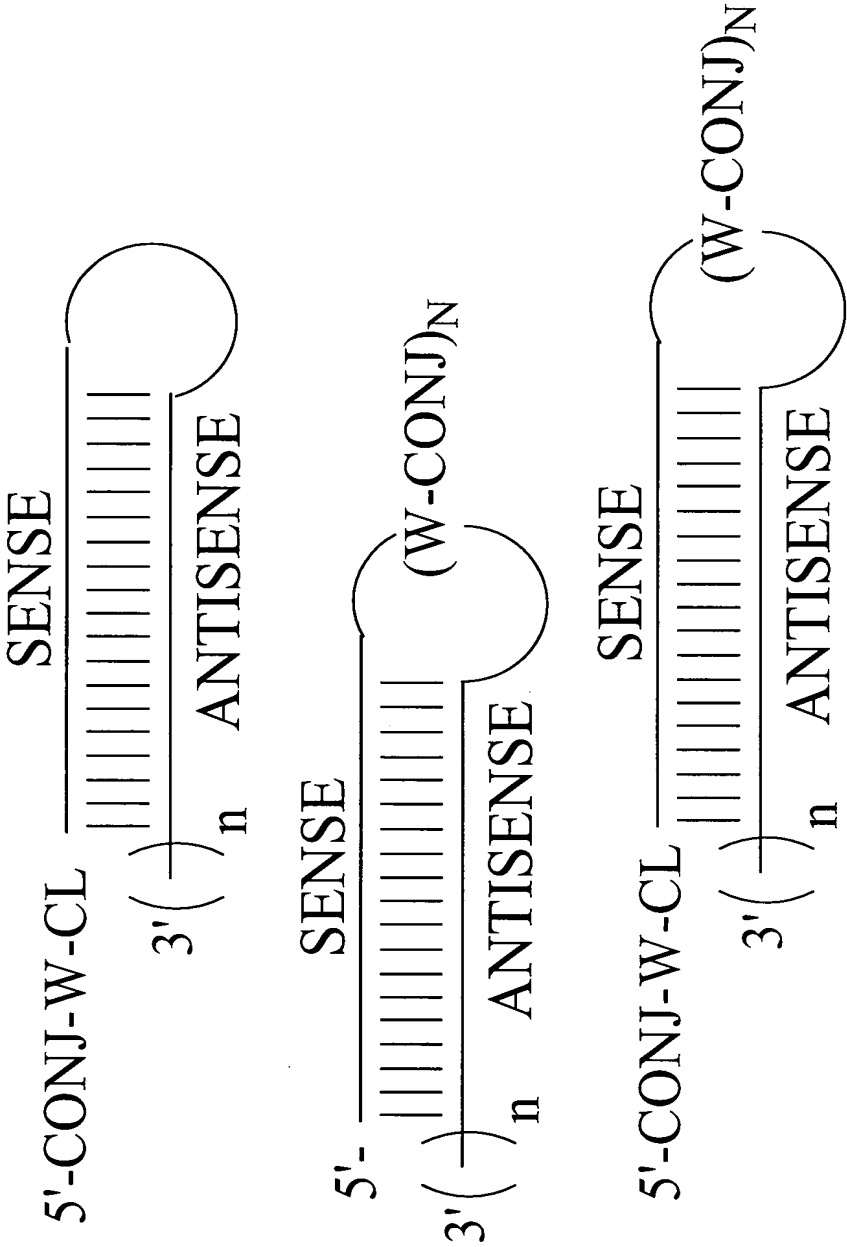
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
 GAL=GALACTOSAMINE; e.g. compounds having Formulae 51-56, 86, 92, 99, 100, 103, 105, 106
 W= linker molecule (see for example Formulae 102 or 103)
 n = integer, e.g. 1, 2, or 3
 N=integer, e.g. 1, 2, 3, or 4

Figure 65: Generalized siNA Conjugate Design



CONJ=any biologically active molecule or conjugate as described herein
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
W= linker molecule
n = integer, e.g. 1, 2, or 3

Figure 66: Generalized siNA Conjugate design



CONJ=any biologically active molecule or conjugate as described herein
CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present
W= linker molecule
n = integer, e.g. 1, 2, or 3
N=integer, e.g. 1, 2, 3, or 4

Figure 67: Distribution of Intact siNA in Liver After SC Administration of Conjugated or Unconjugated Chemistries

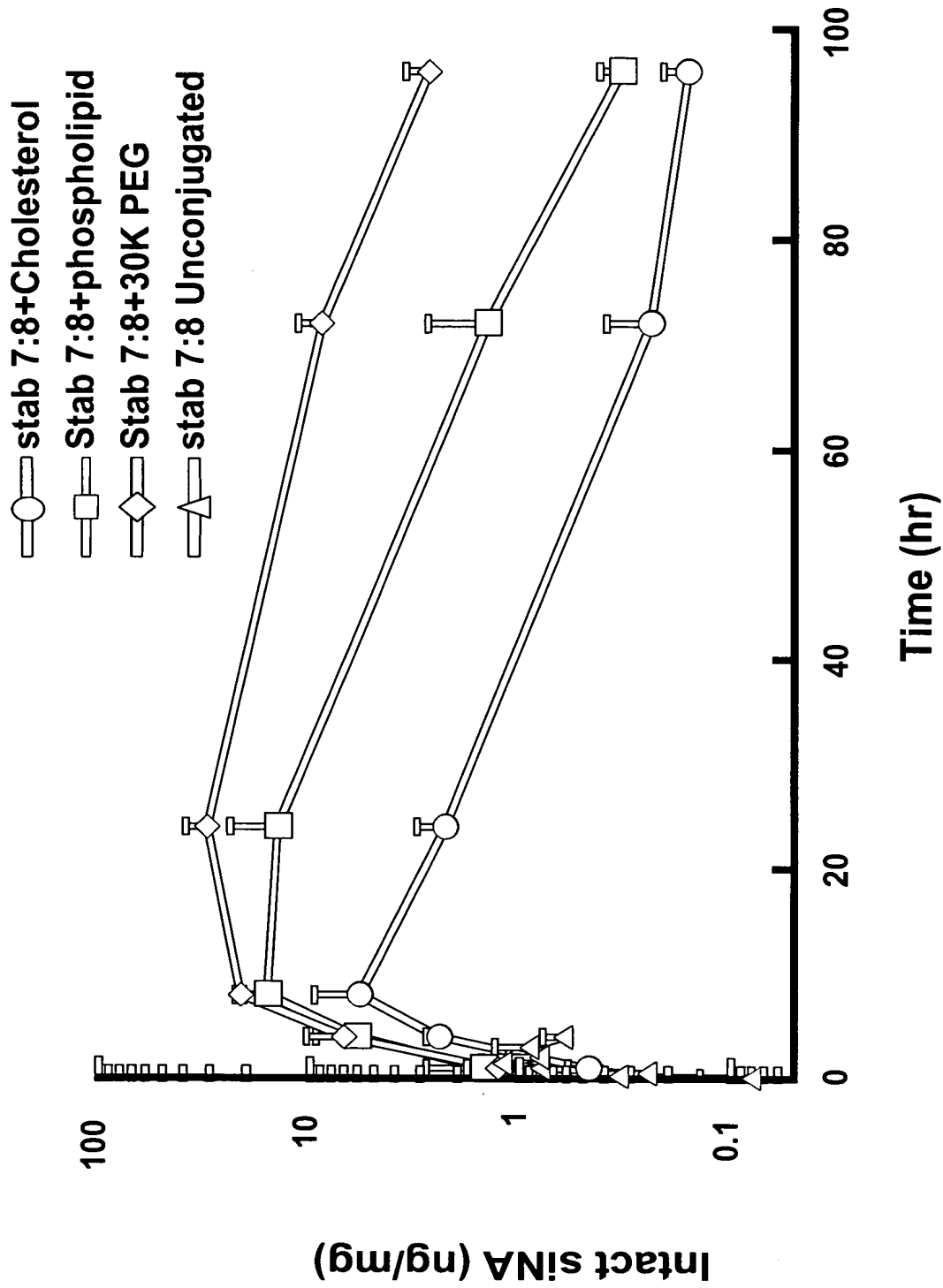


Figure 68: Lipid Free Delivery of HBV siNA Conjugates in Cell Culture

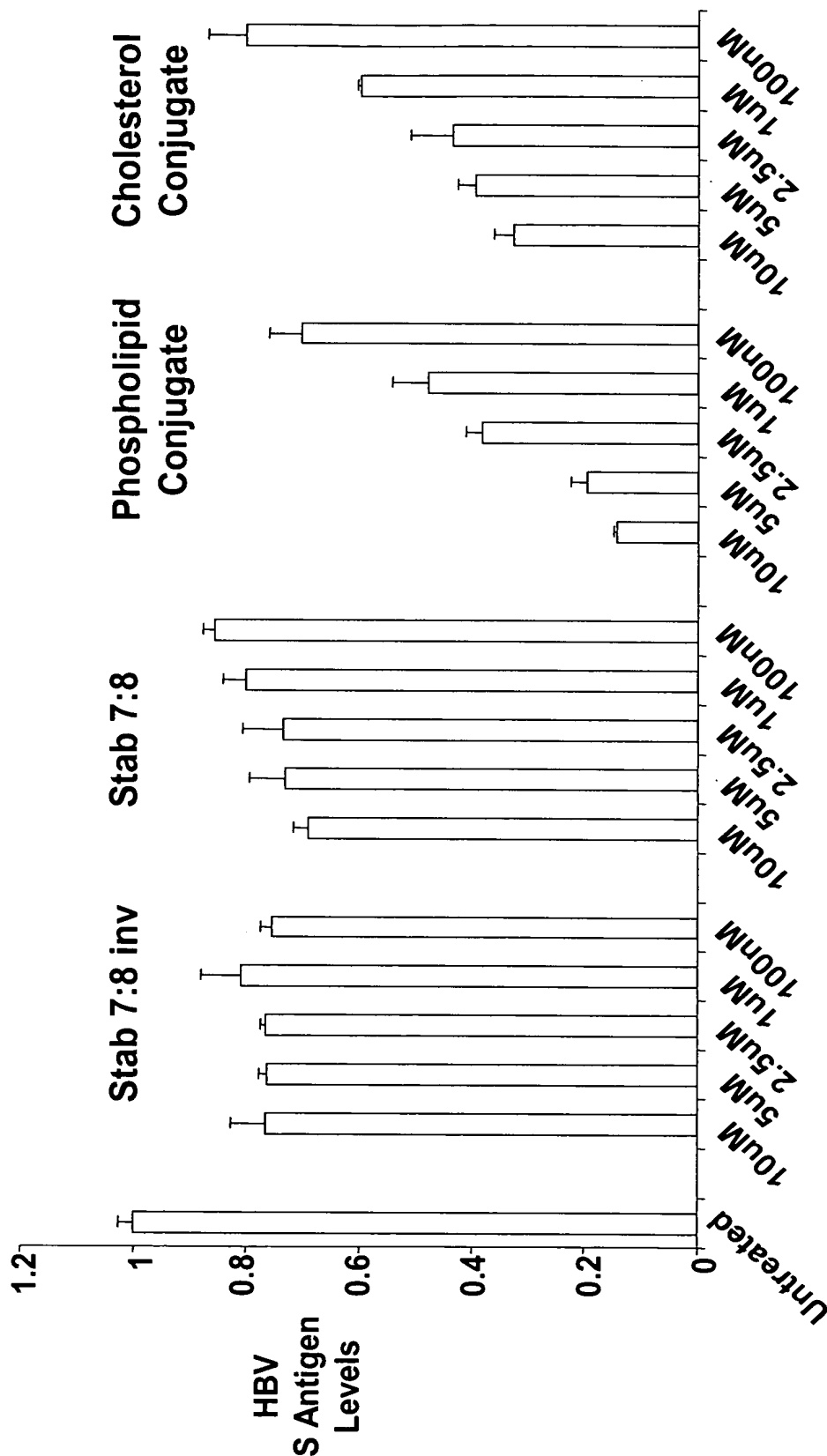


Figure 69: Scale-up of "mono" Galactosamine phosphoramidite

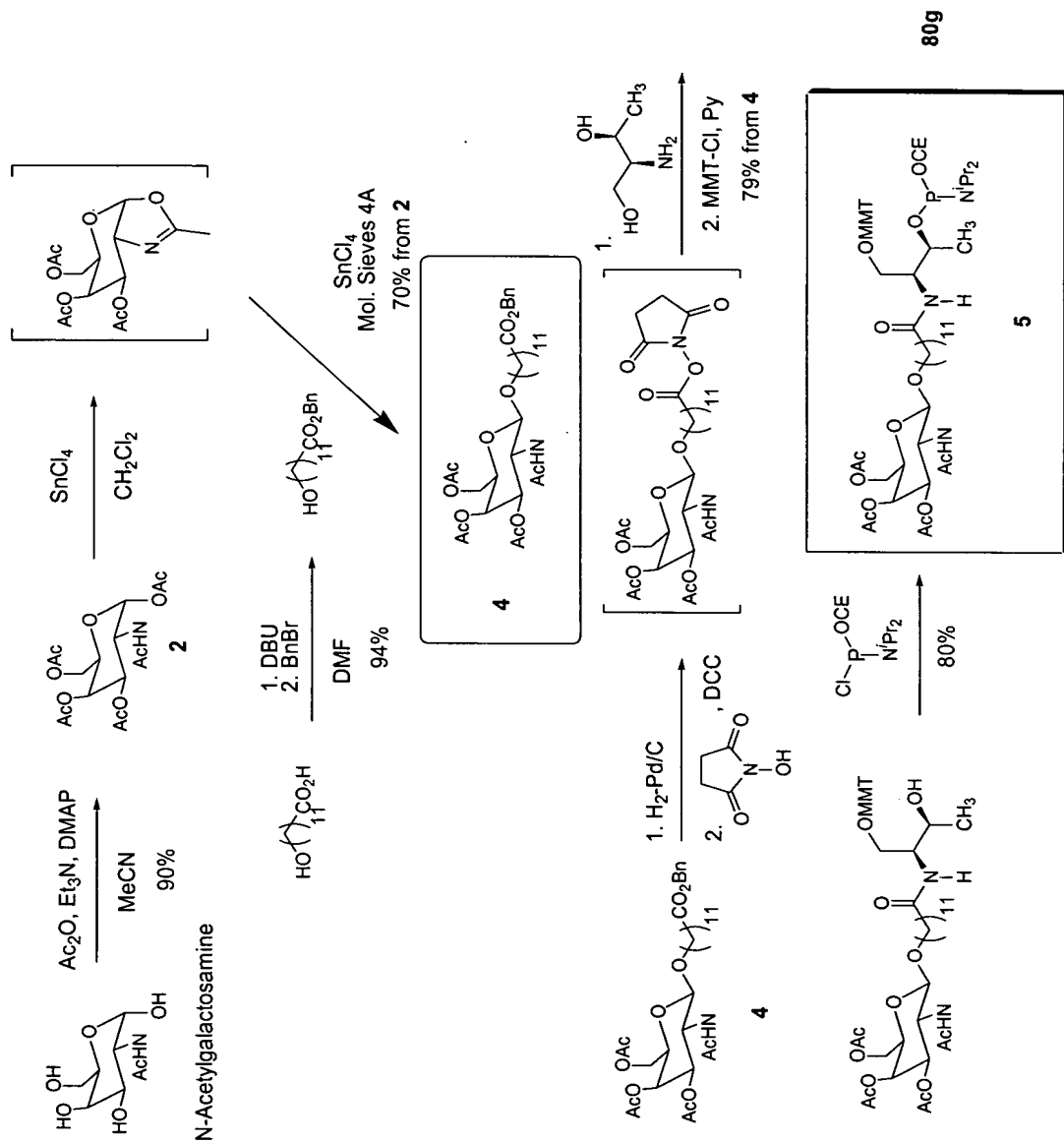


Figure 70: Synthesis of “tri” Galactosamine phosphoramidite

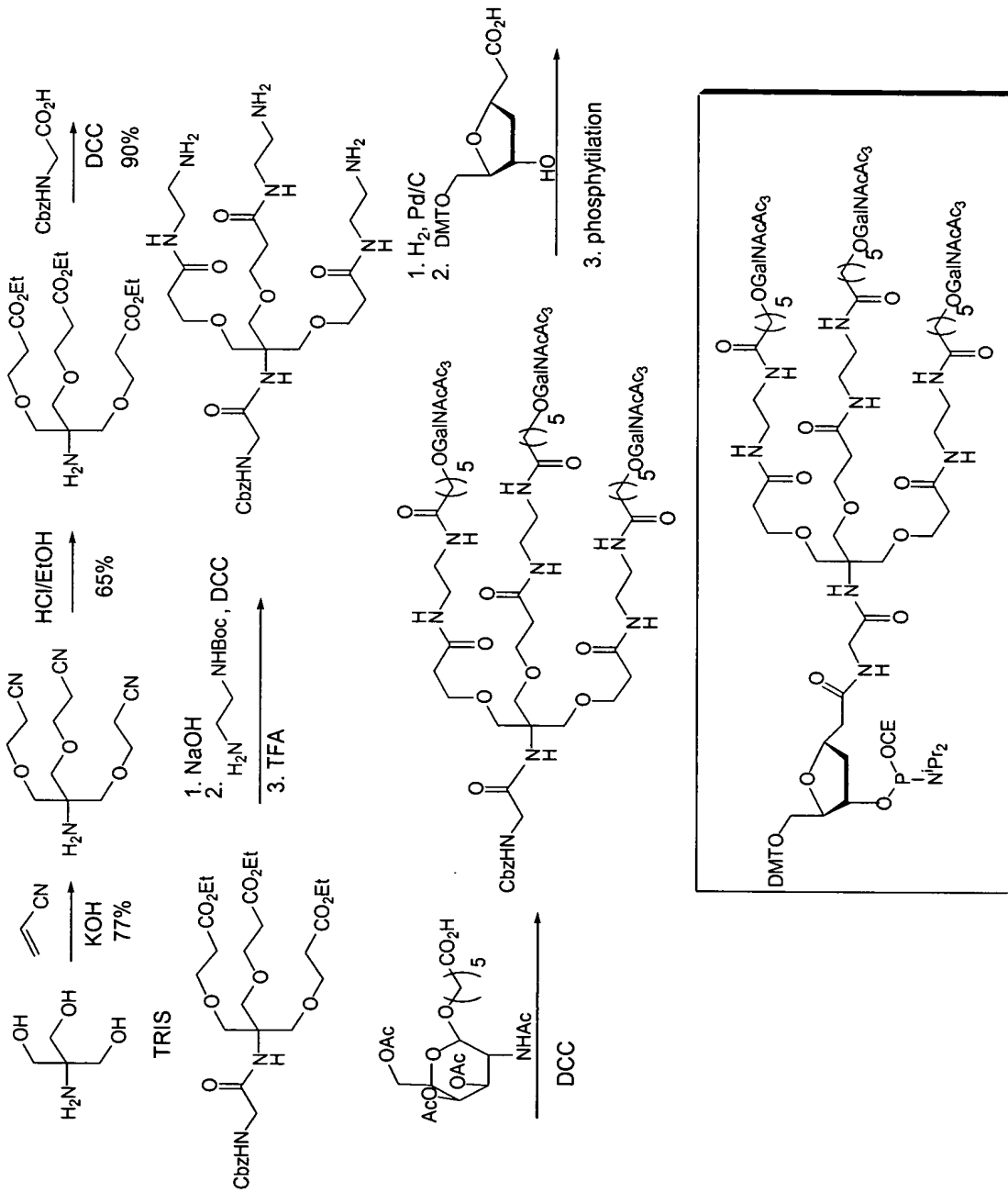


Figure 71: Synthesis of another Tri-Galactosamine Conjugate

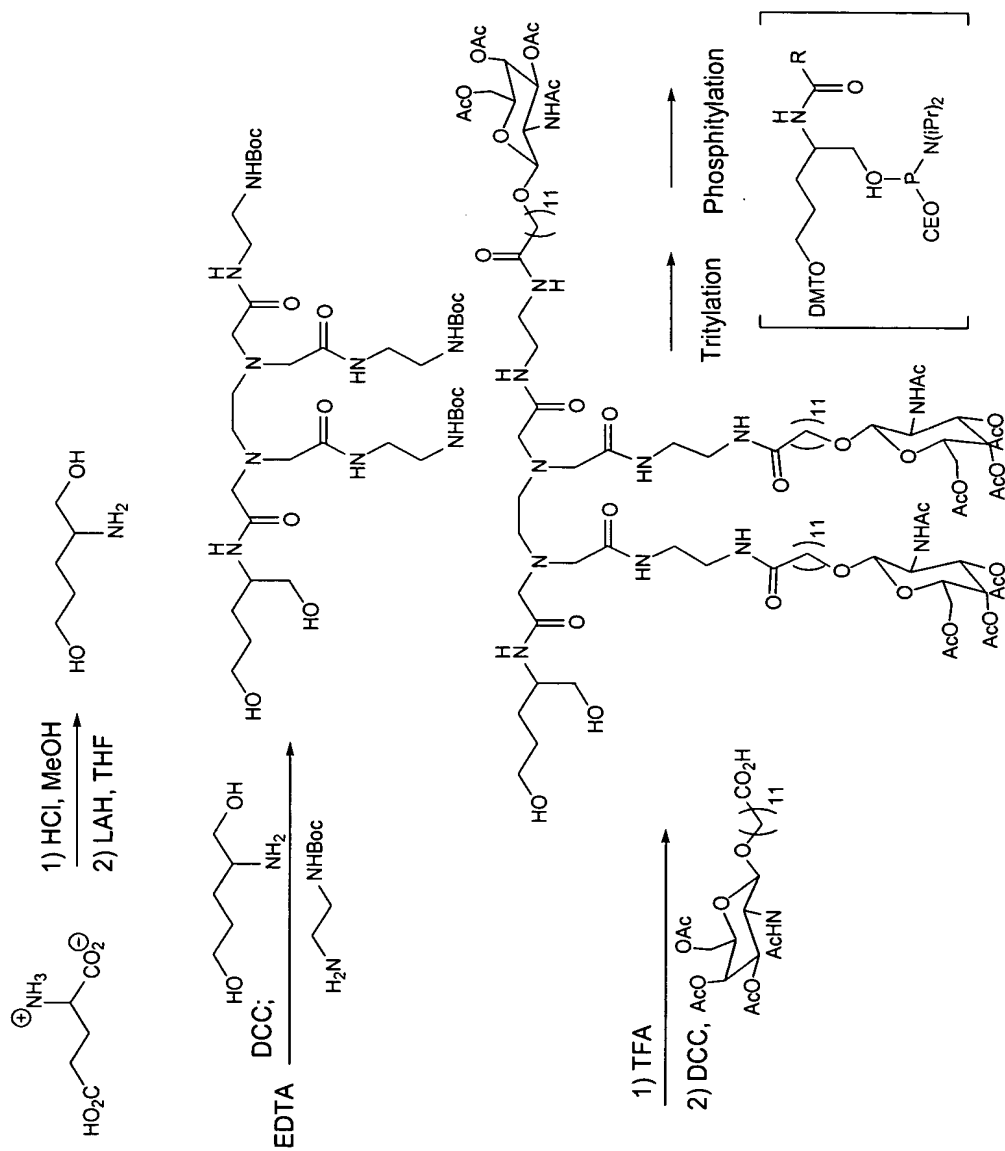


Figure 72: Alternate Synthesis of Tri-Galactosamine Conjugate

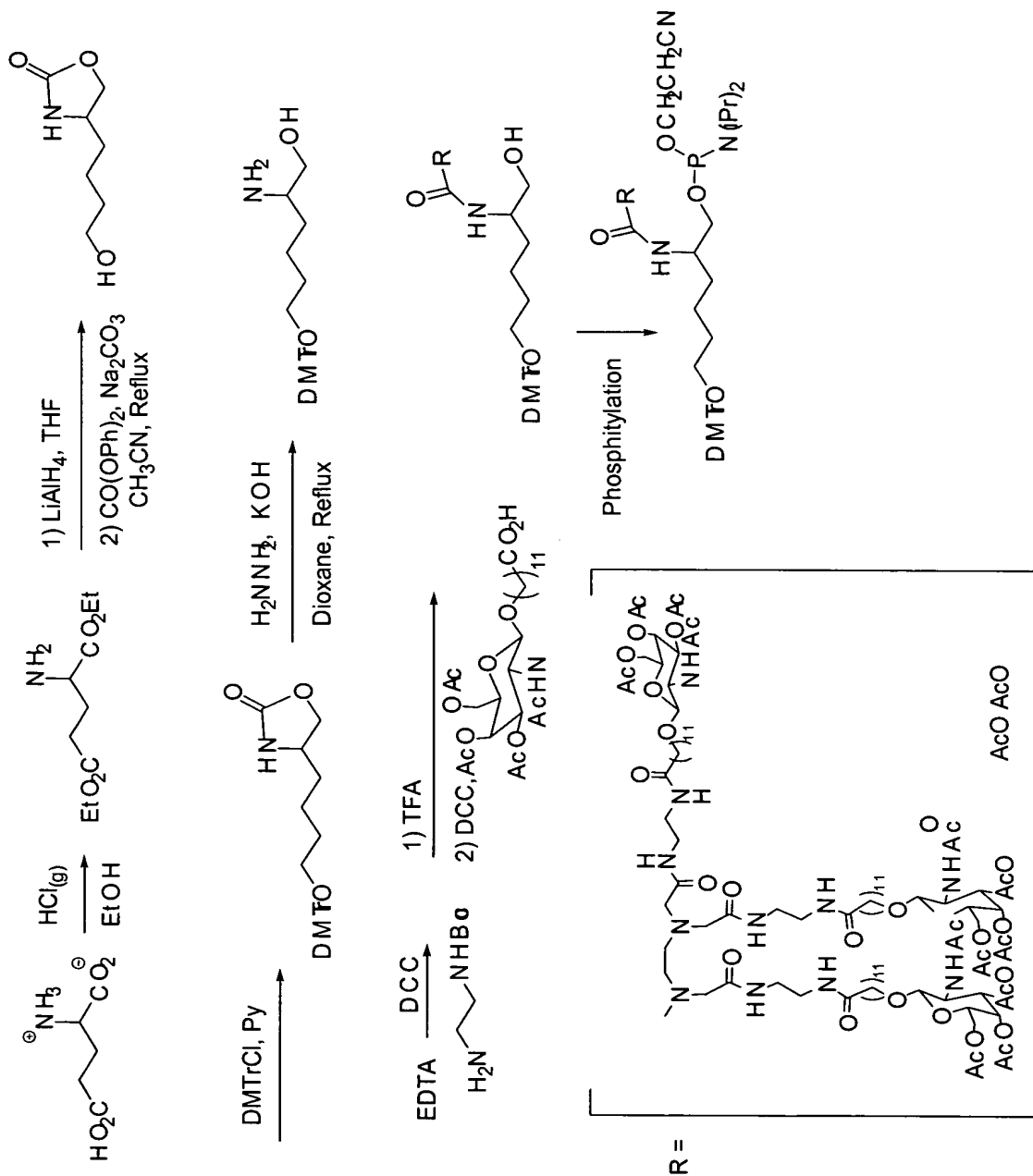
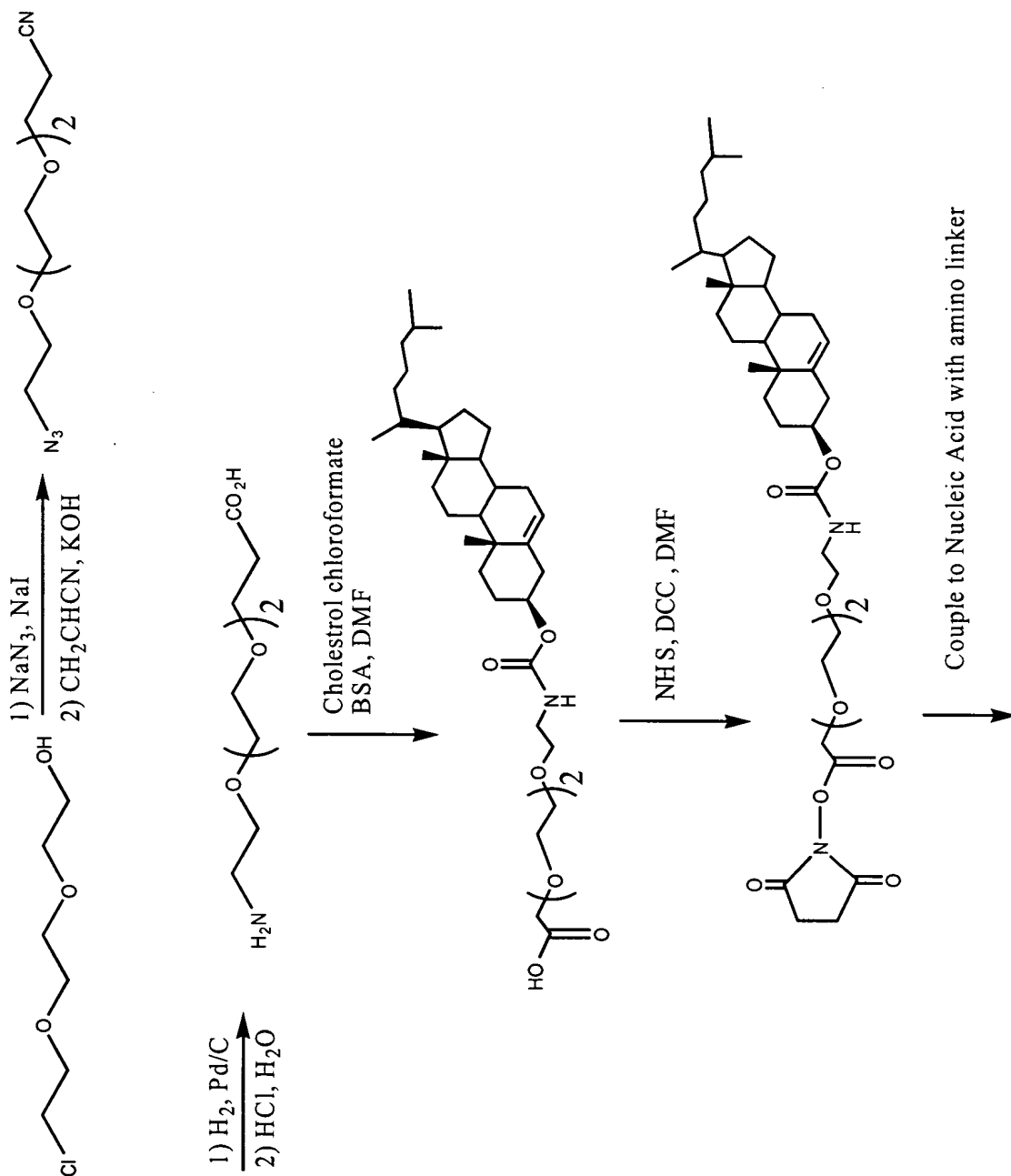
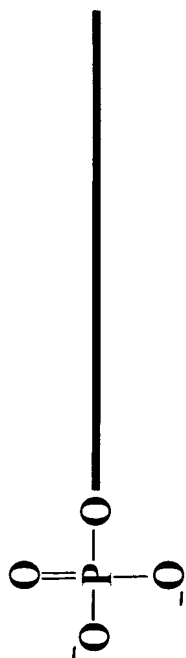
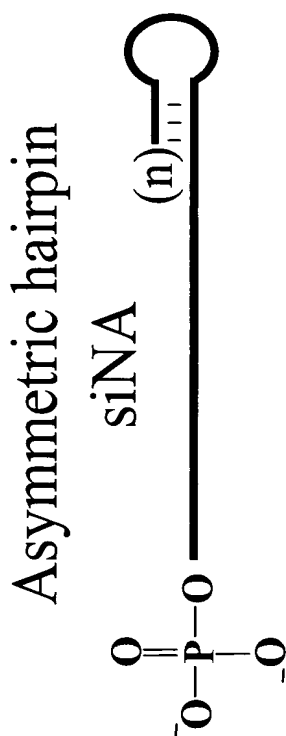
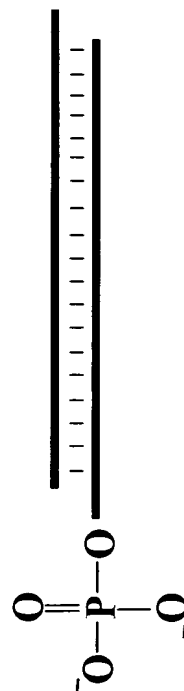


Figure 73: Synthesis of NHS Cholesterol Conjugate





Phosphates can be modified as described herein



Asymmetric duplex siNA

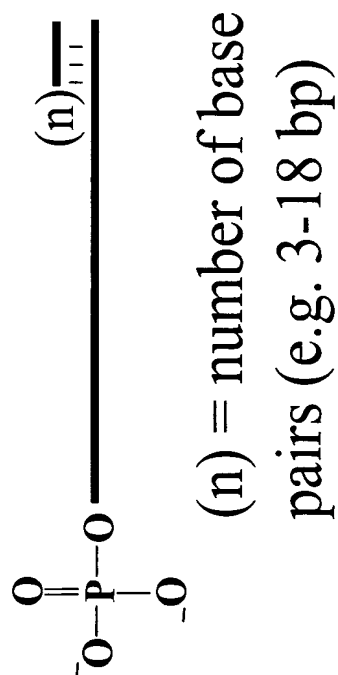


Figure 75: 5'-phosphate modifications

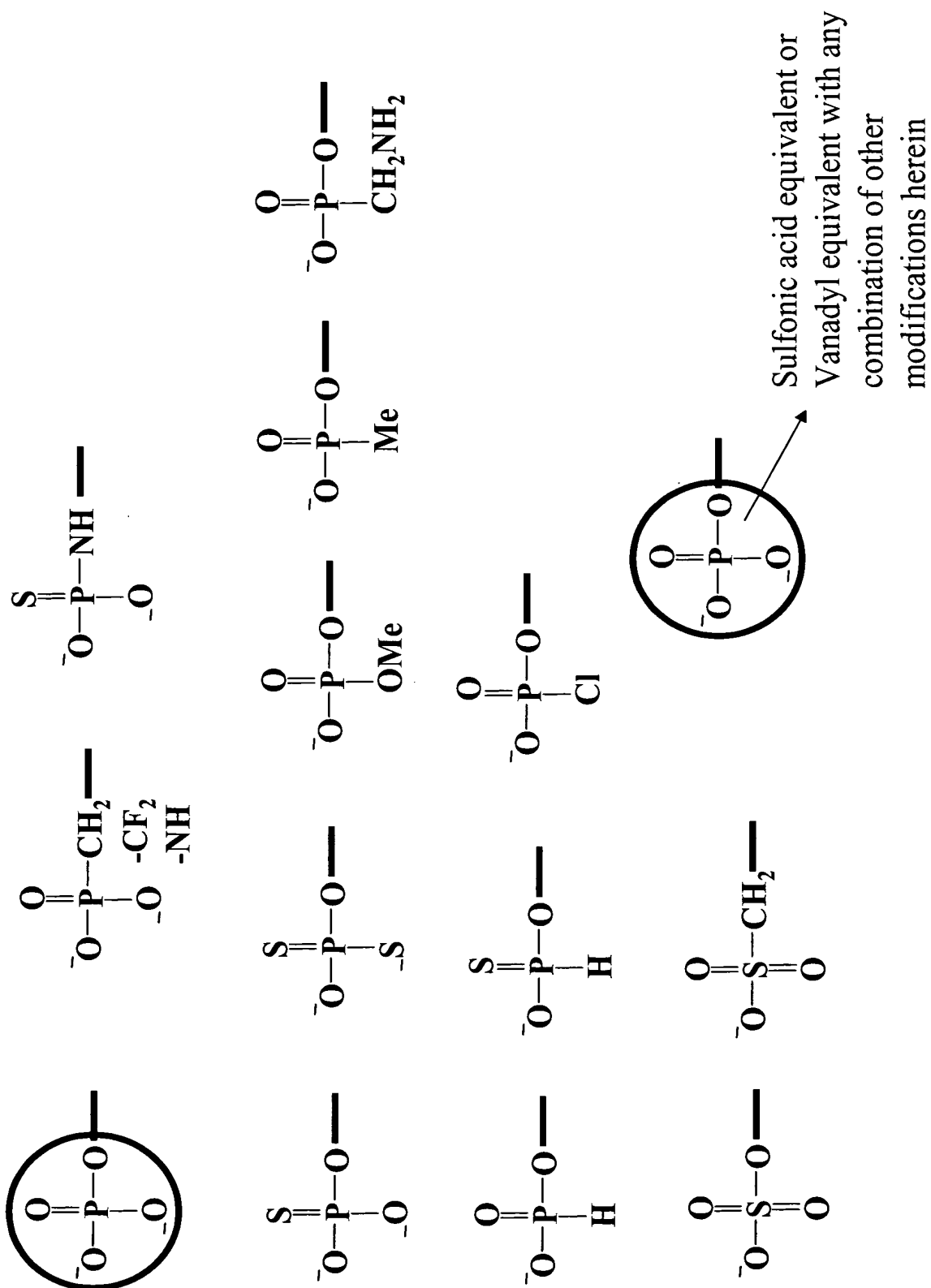


Figure 76: siNA Targeting VEGFR-1 Inhibits VEGF-Induced Rat Corneal Angiogenesis

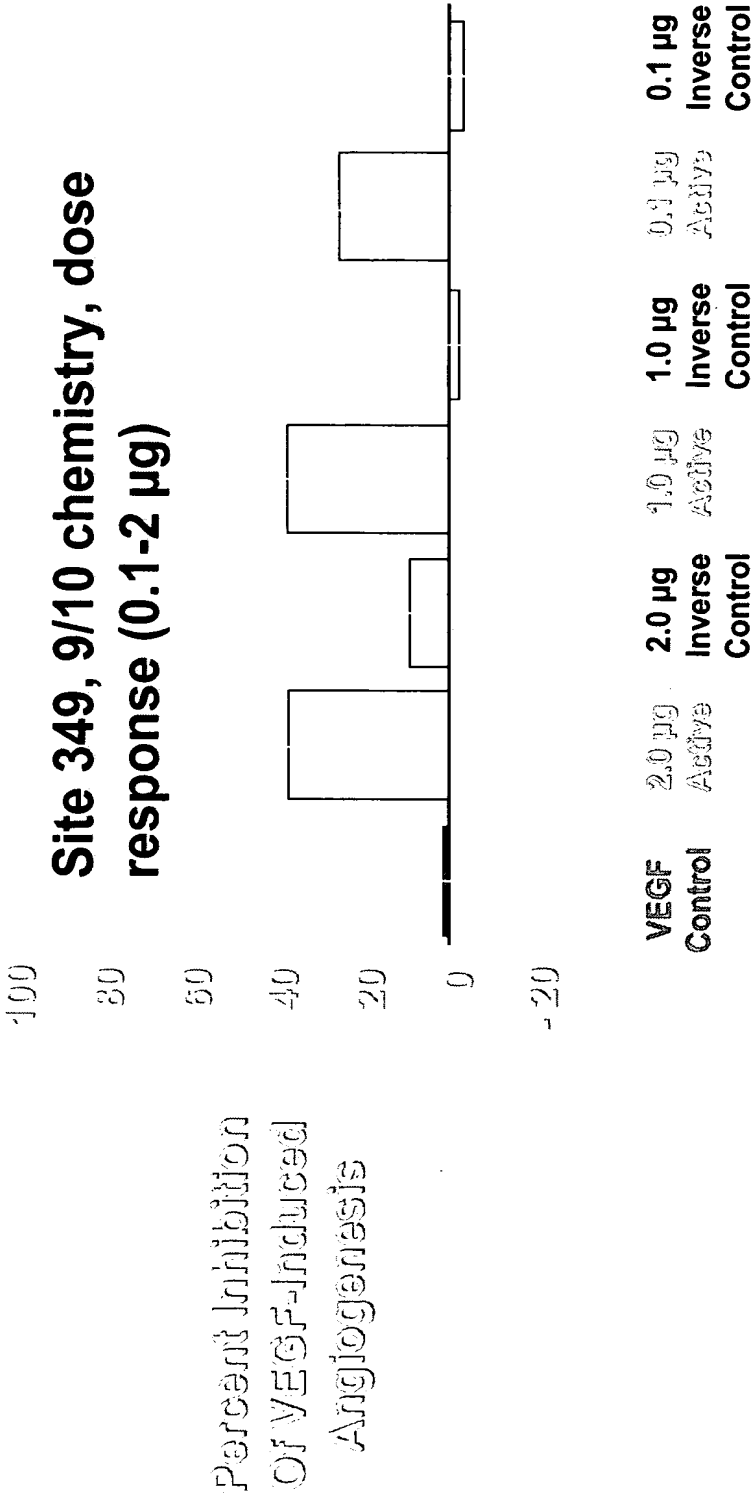


Figure 77: Duration of Effect of Modified siNA Constructs

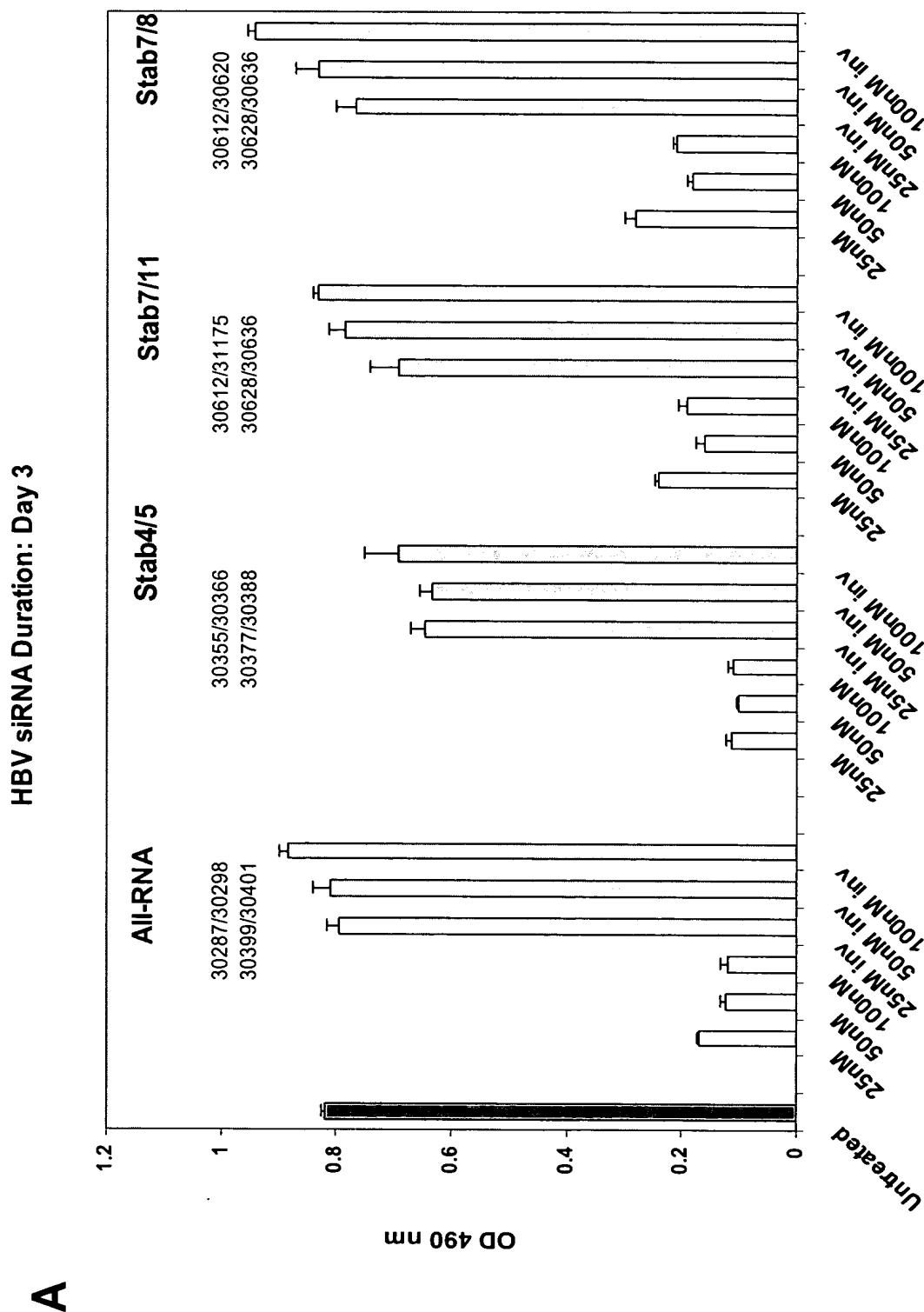


Figure 77: Duration of Effect of Modified siNA Constructs

HBV siRNA Duration: Day 9

B

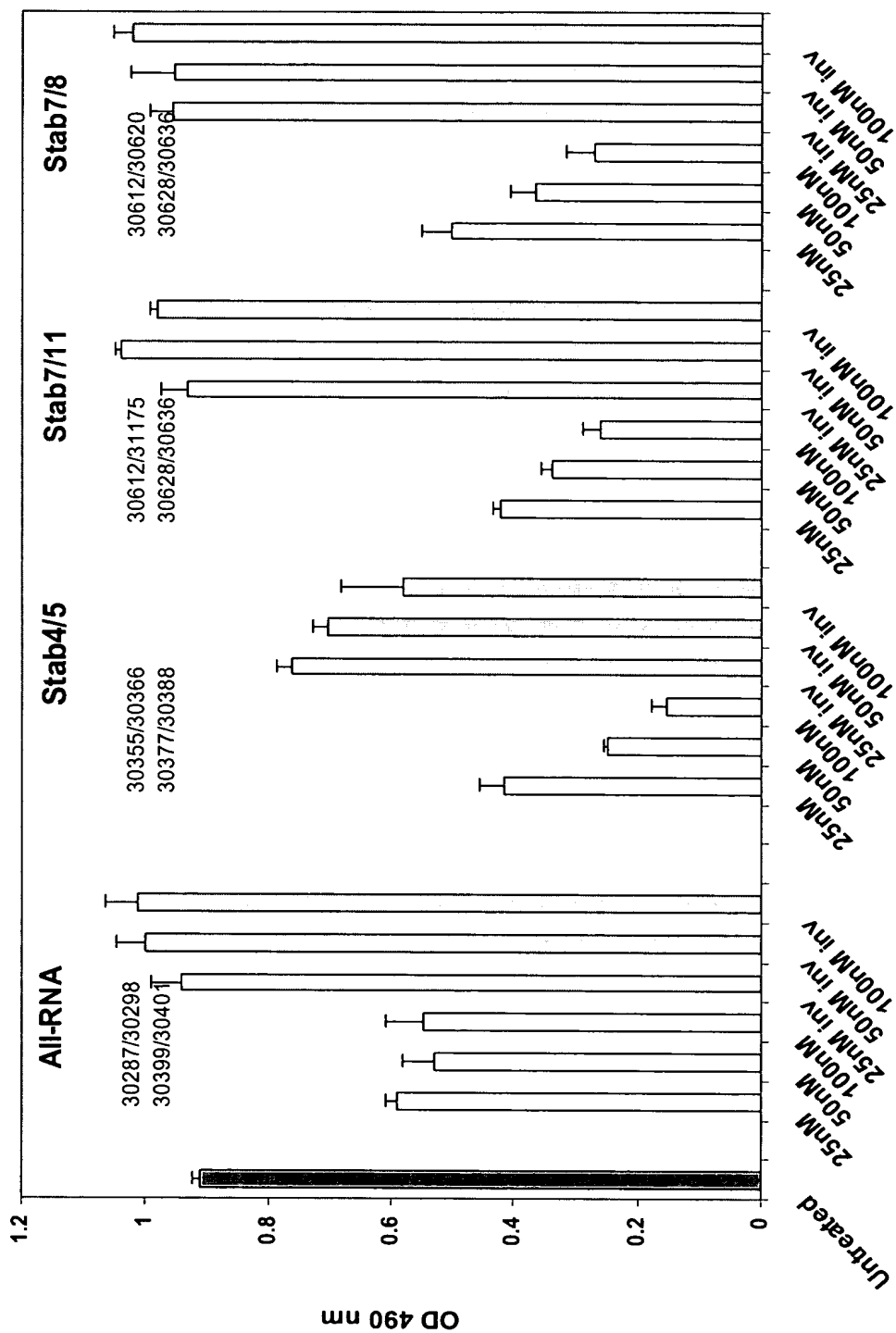


Figure 77: Duration of Effect of Modified siNA Constructs

HBV siRNA Duration: Day 21

C

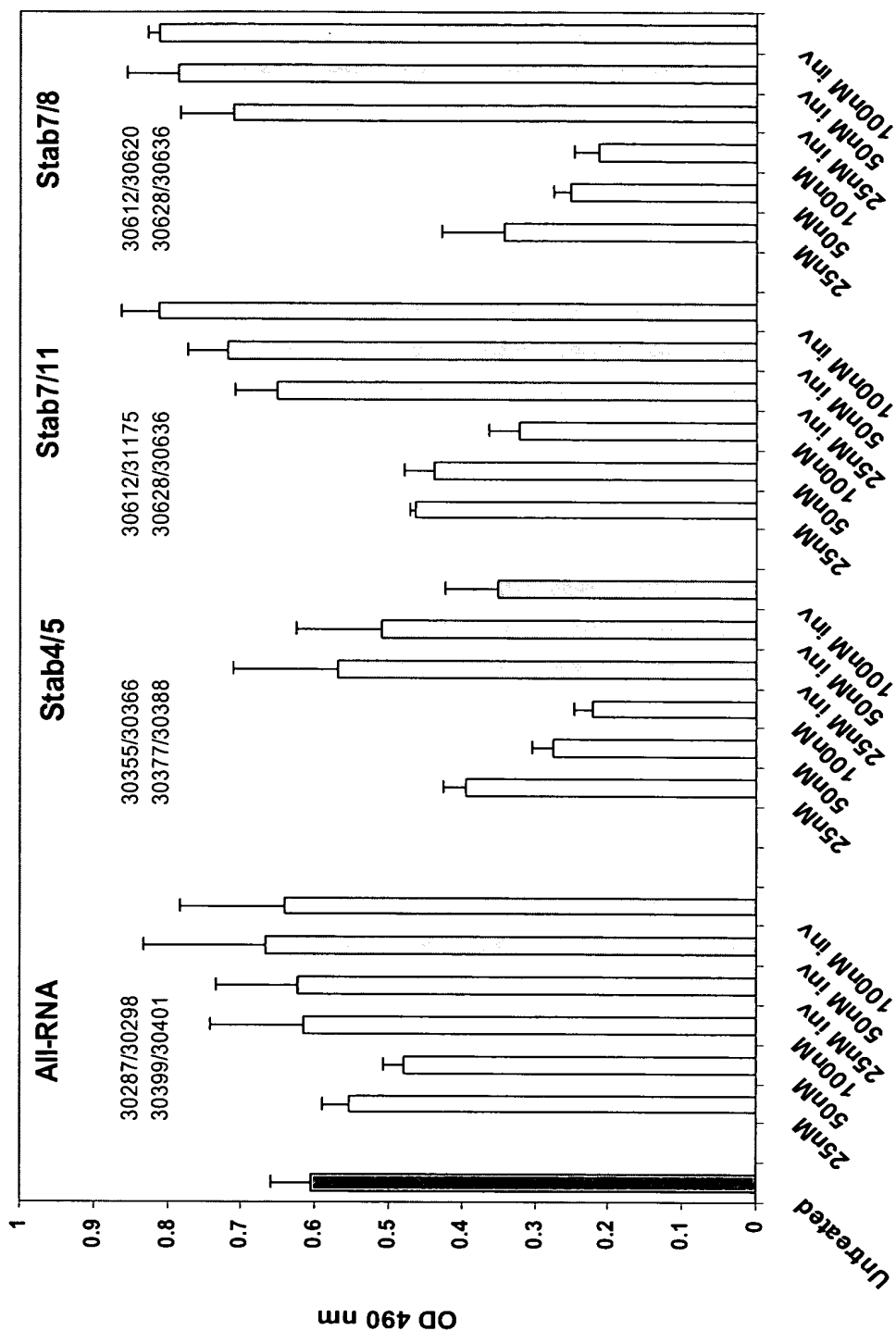


Figure 77: Duration of Effect of Modified siNA Constructs

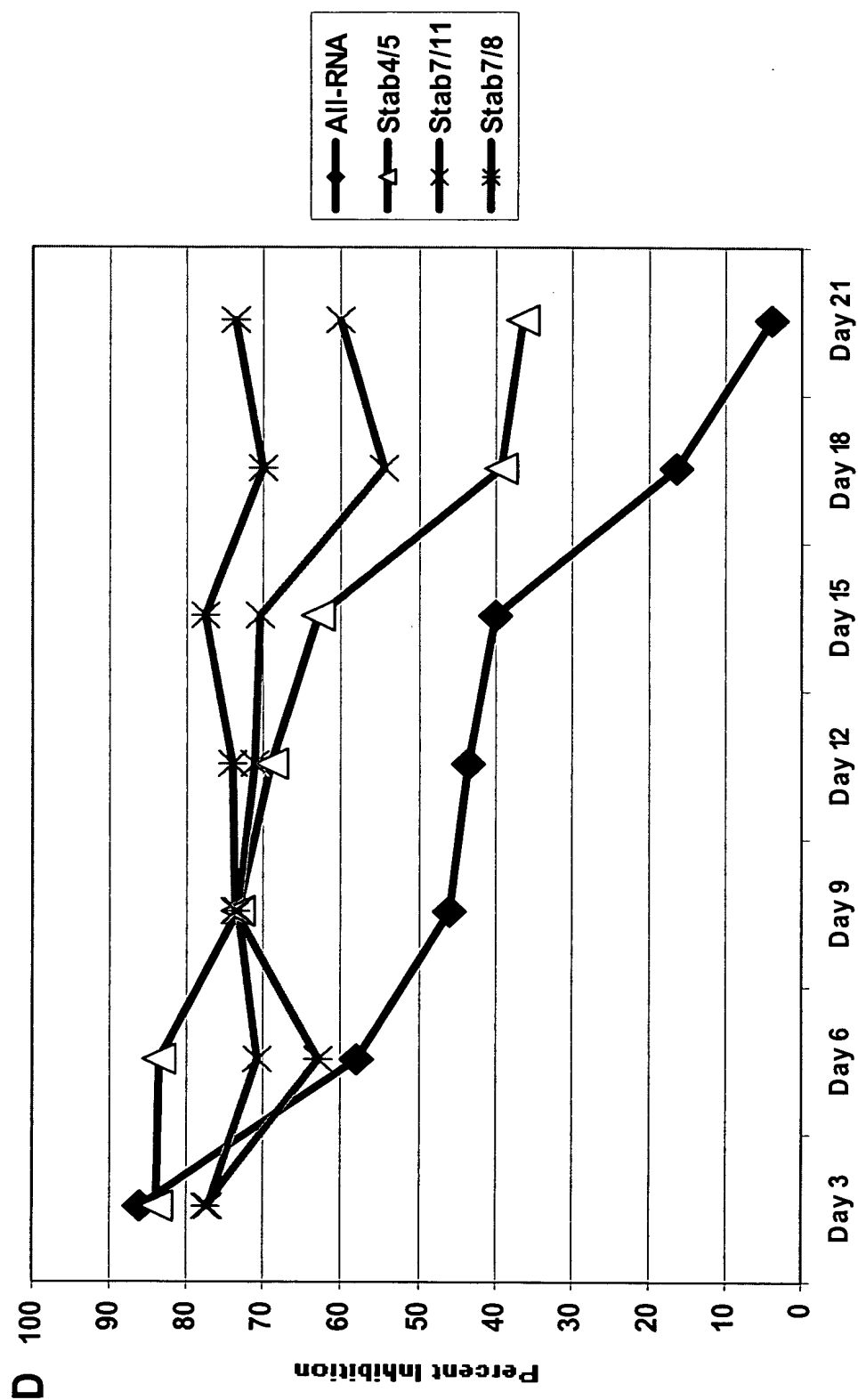


Figure 77: Duration of Effect of Modified siNA Constructs

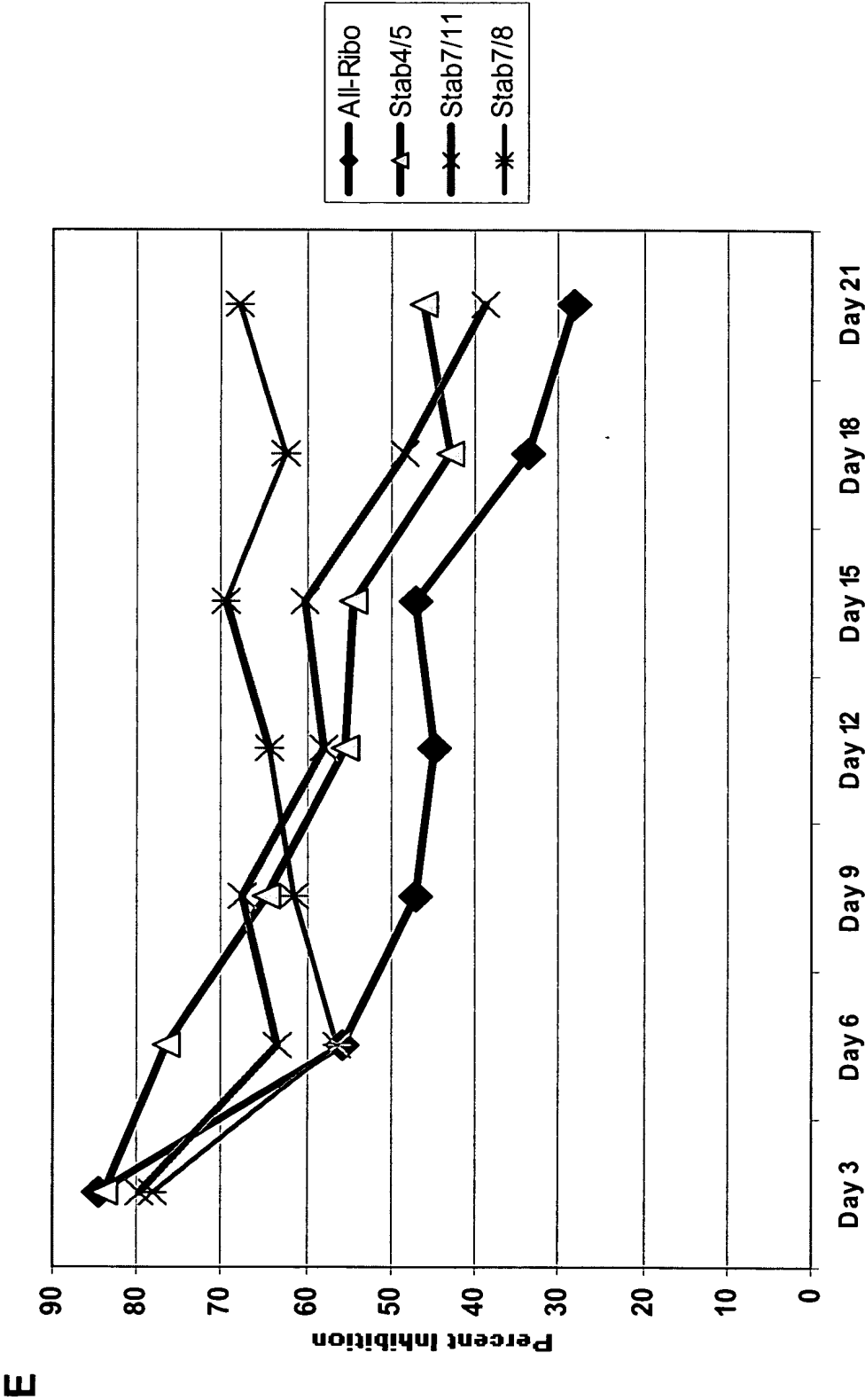


Figure 77: Duration of Effect of Modified siNA Constructs

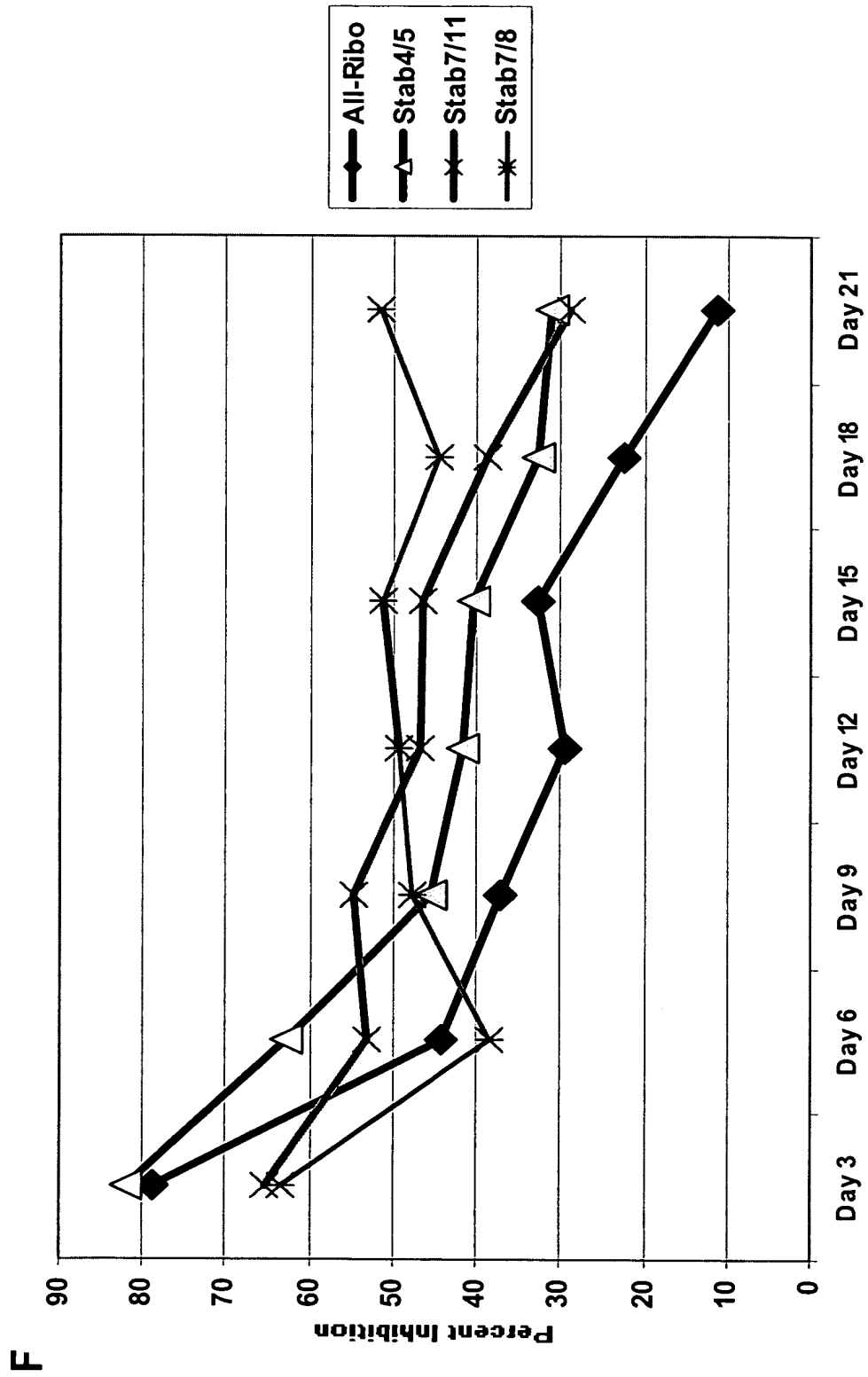
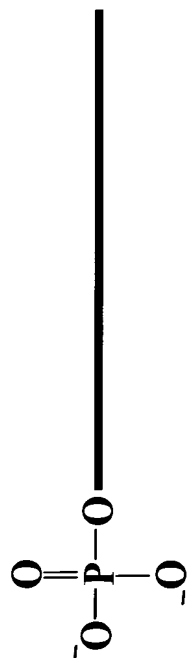
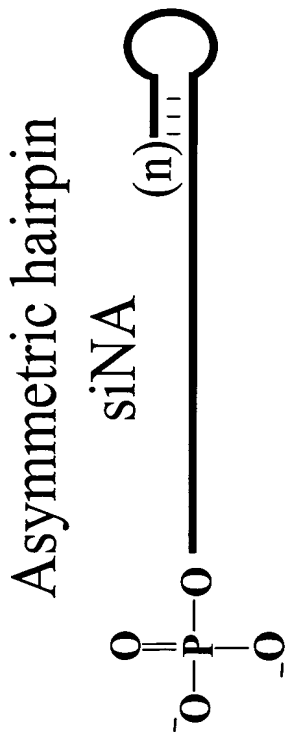
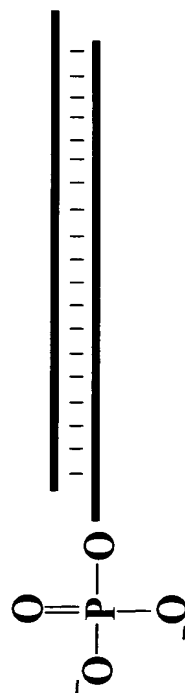


Figure 78: Phosphorylated siNA constructs



Phosphates can be modified
as described herein



Asymmetric duplex
siNA

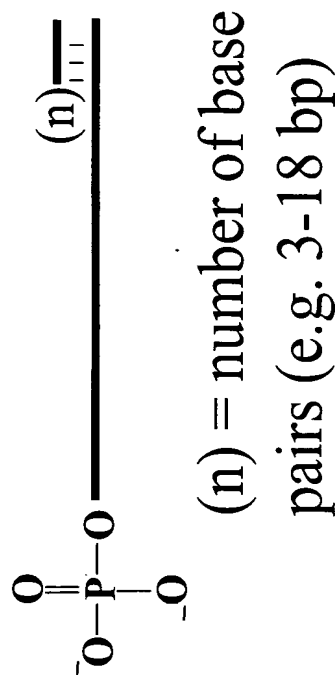
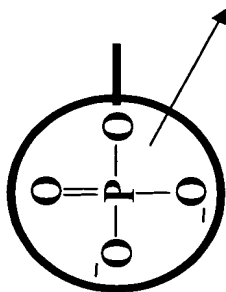
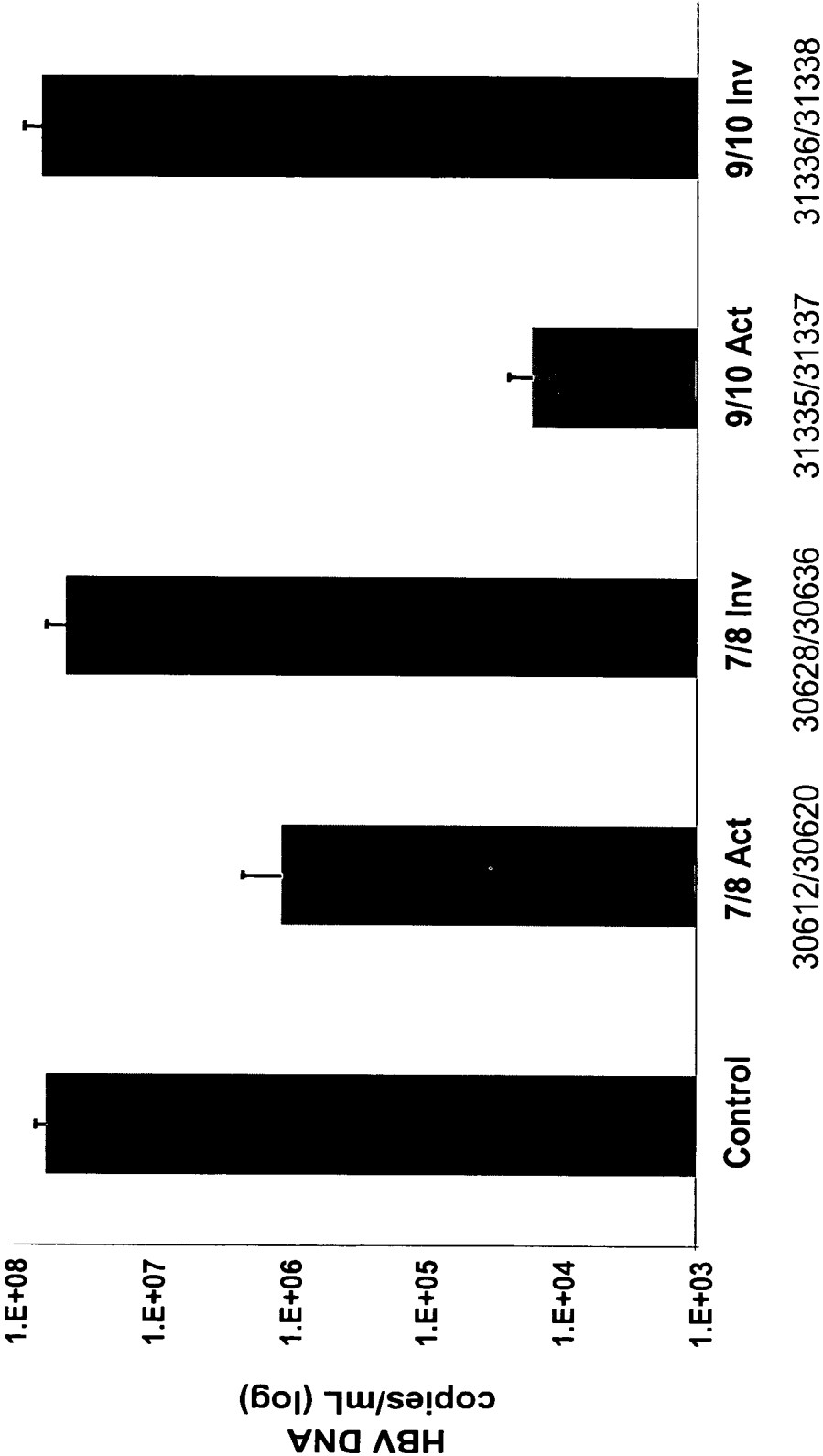


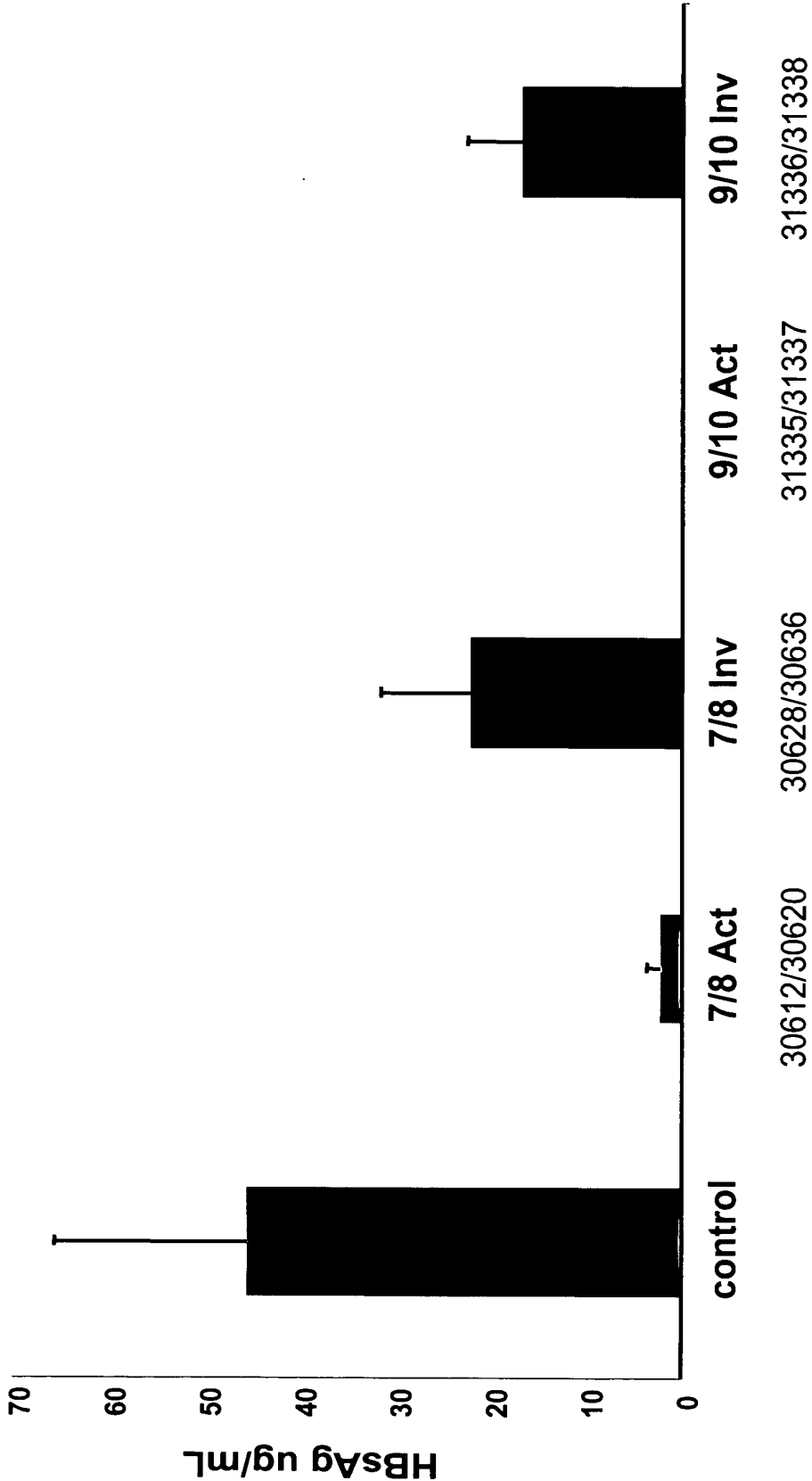
Figure 79: 5'-phosphate modifications



**Figure 80: Serum HBV DNA in Mice Treated
with siNA Via HDI**



**Figure 81: Serum HBsAg in Mice Treated
with siNA Via HDI**



**Figure 82: Liver HBV RNA in Mice Treated
with siNA Via HDI**

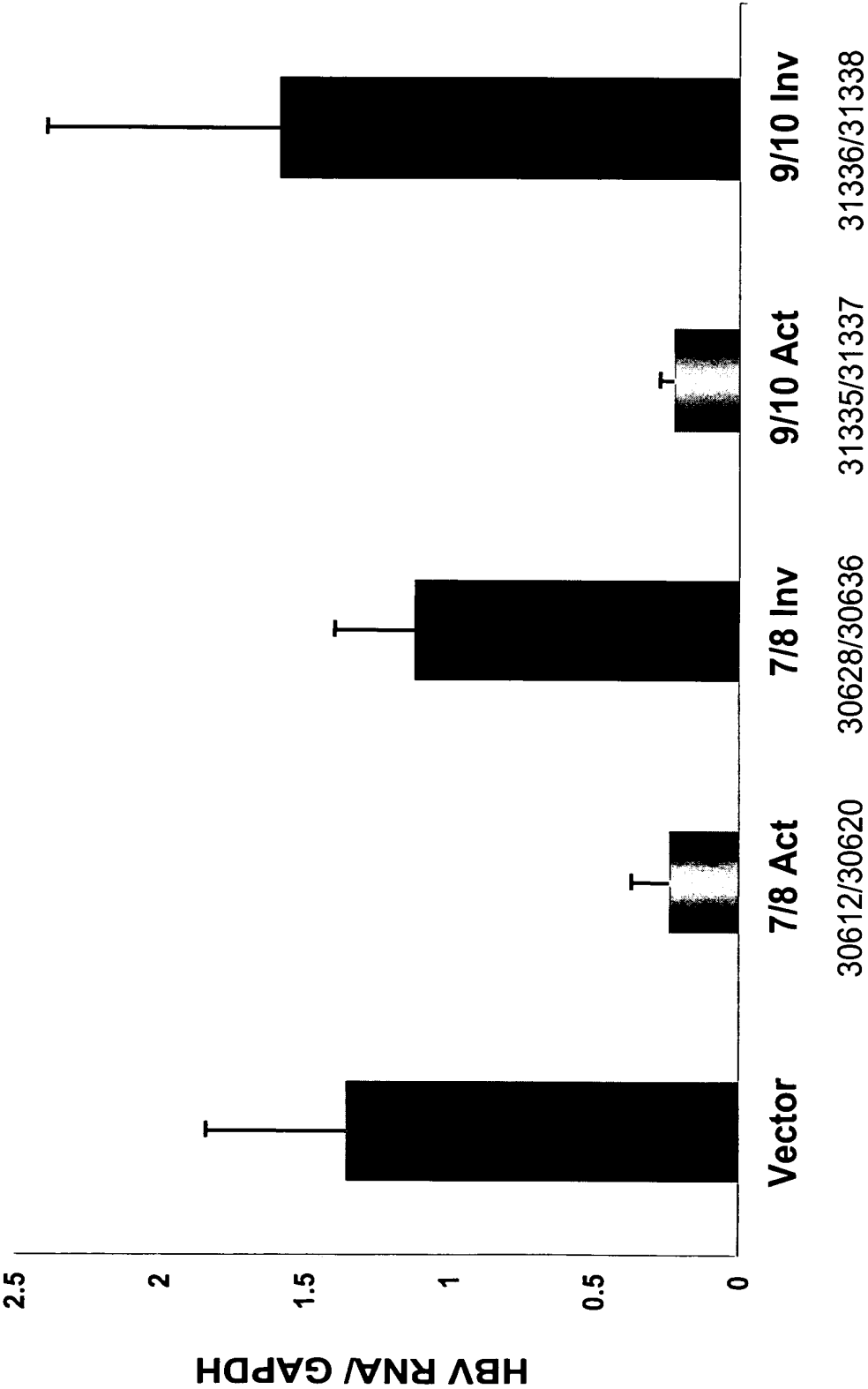
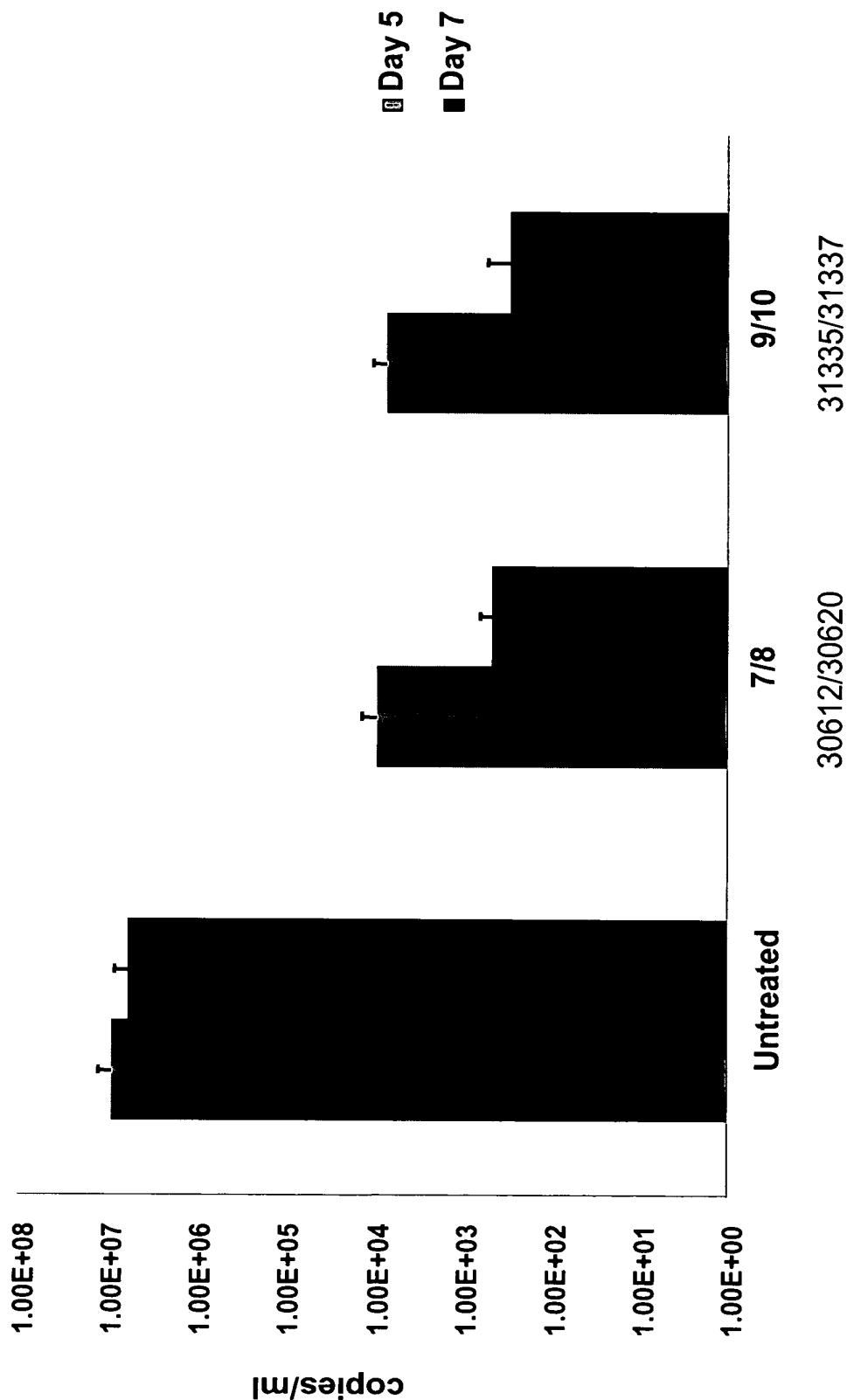
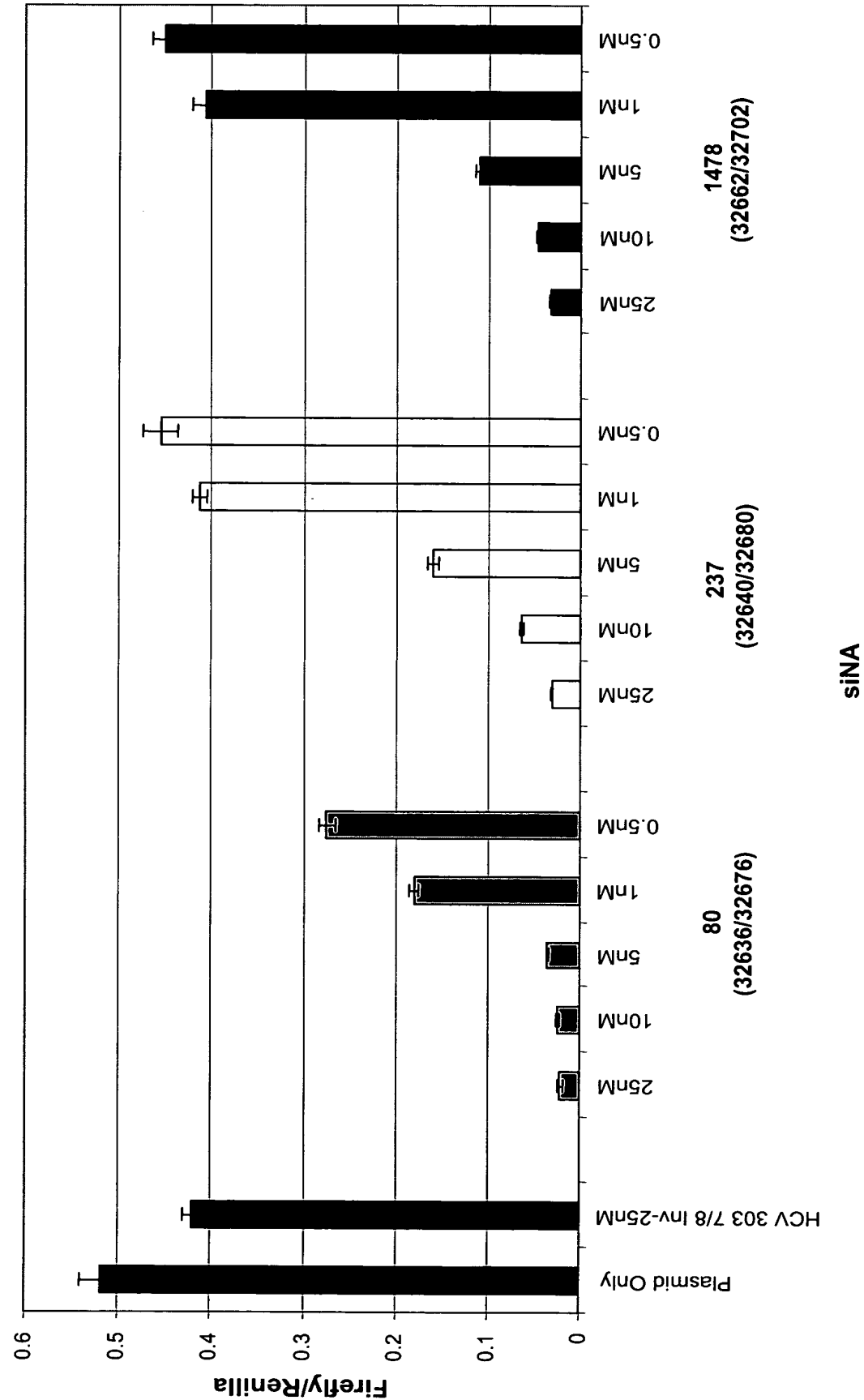


Figure 83: Serum HBV DNA in Mice Treated with siNA Via HDI 5 and 7 days post treatment



**Figure 84: Luciferase Dose Response
of select active siNA constructs**



**Figure 85: Luciferase Dose Response
 of select active siNA constructs**

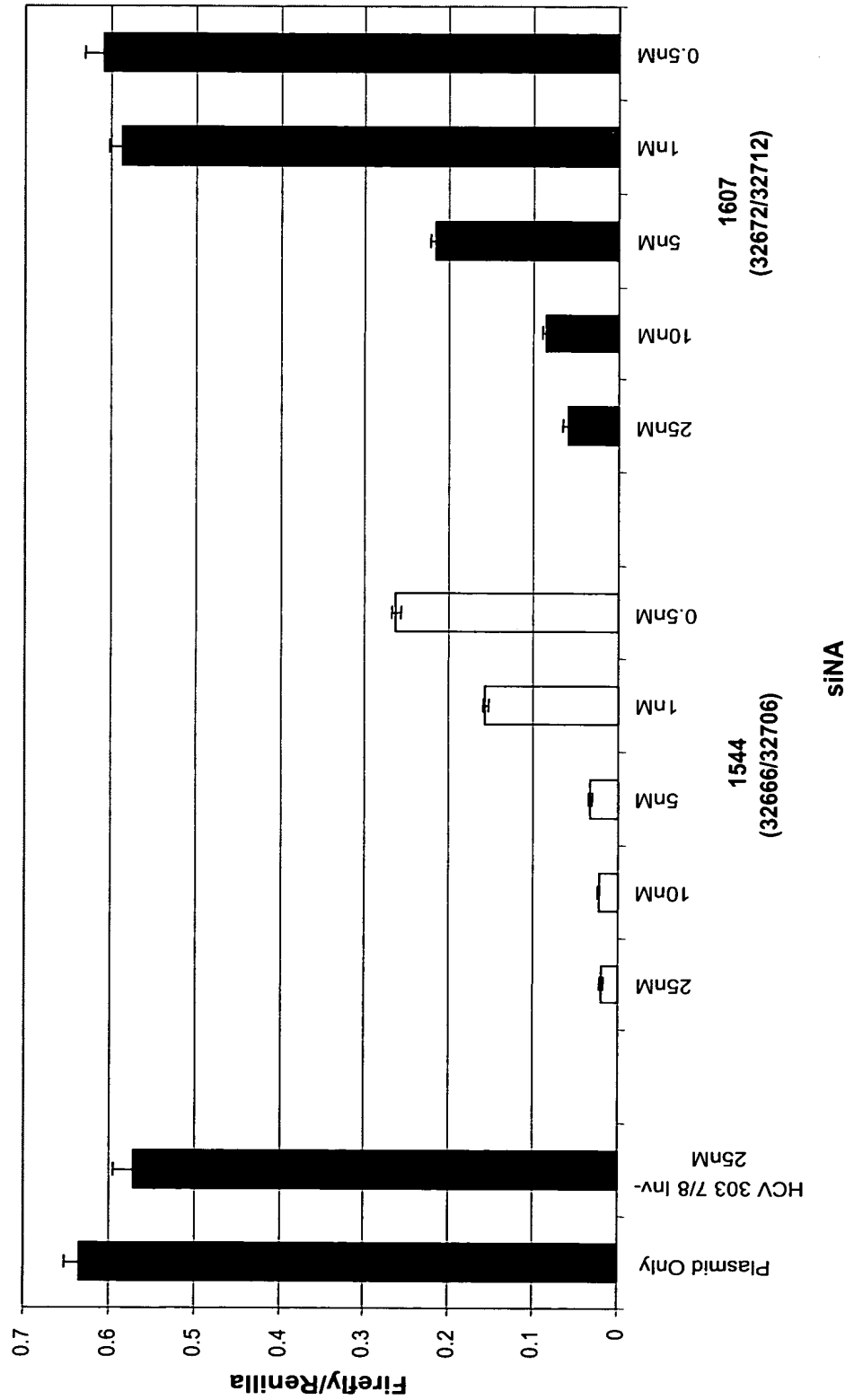
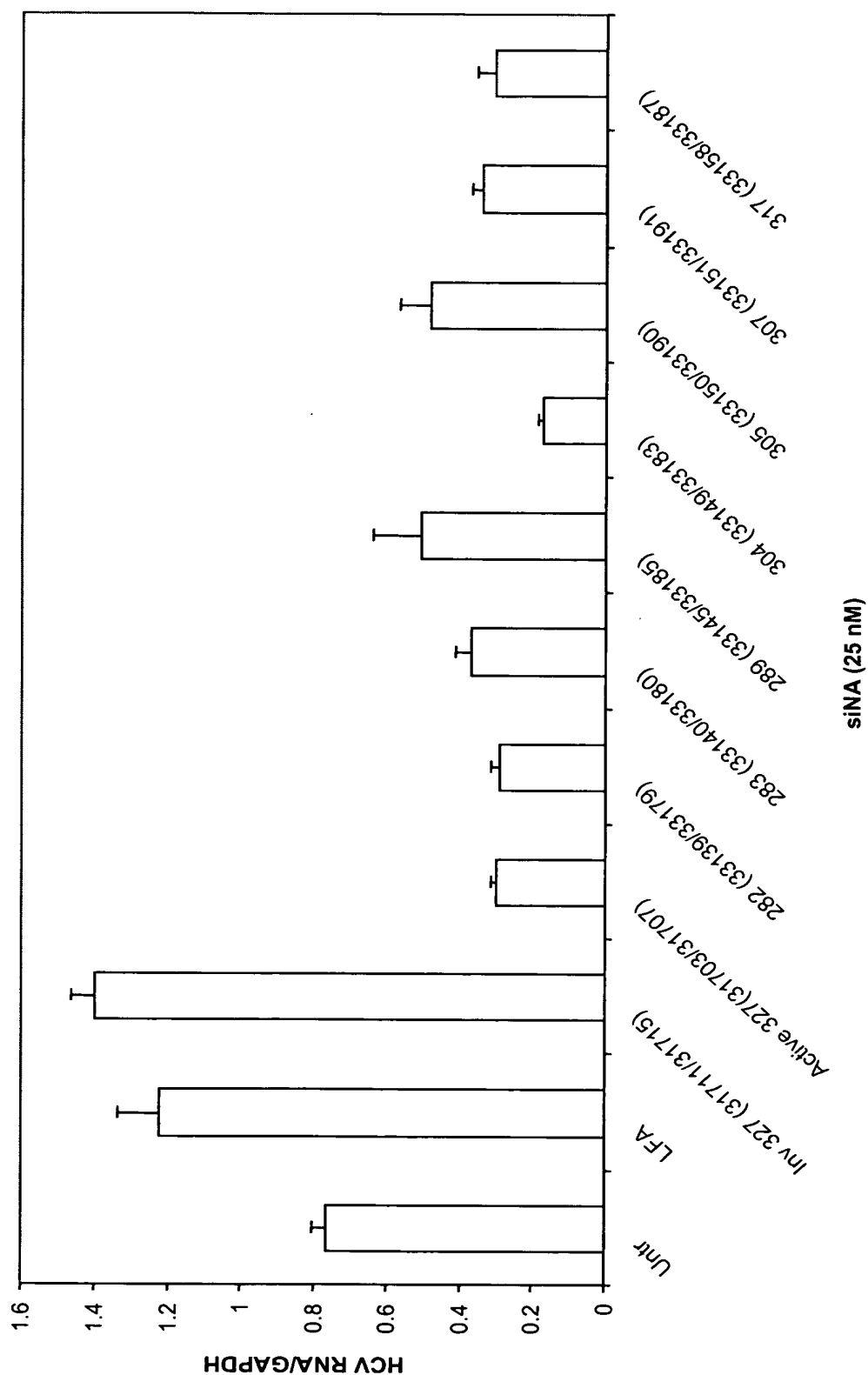


Figure 86: Activity of Stab 7/8 Stabilized siNAs in HCV Replicon



**Figure 87: Activity of Stabilized 7/8 siNAs Against HBV
in HepG2 Cells**

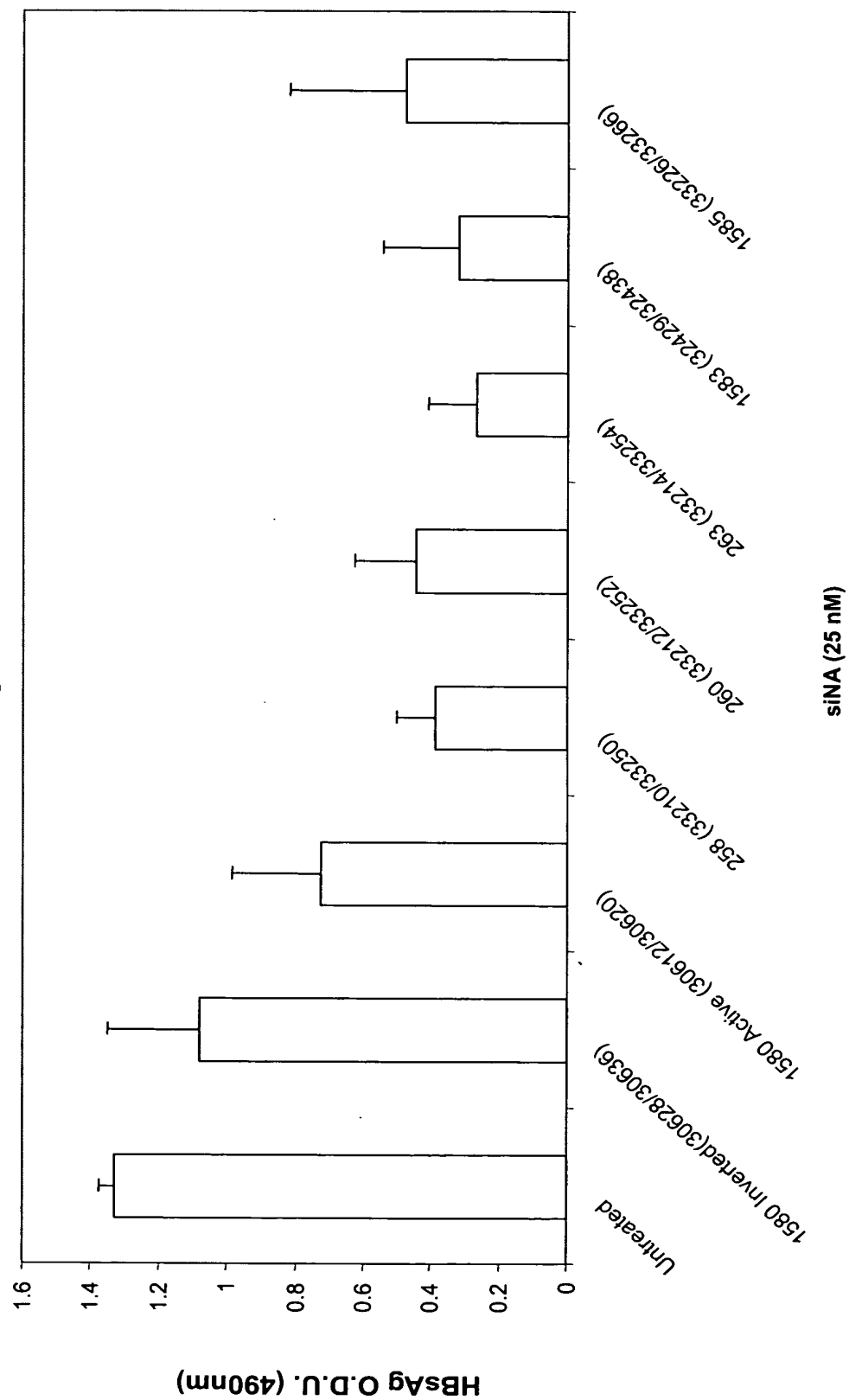


Figure 88: HBV/siNA to site 1580 Combination Constructs

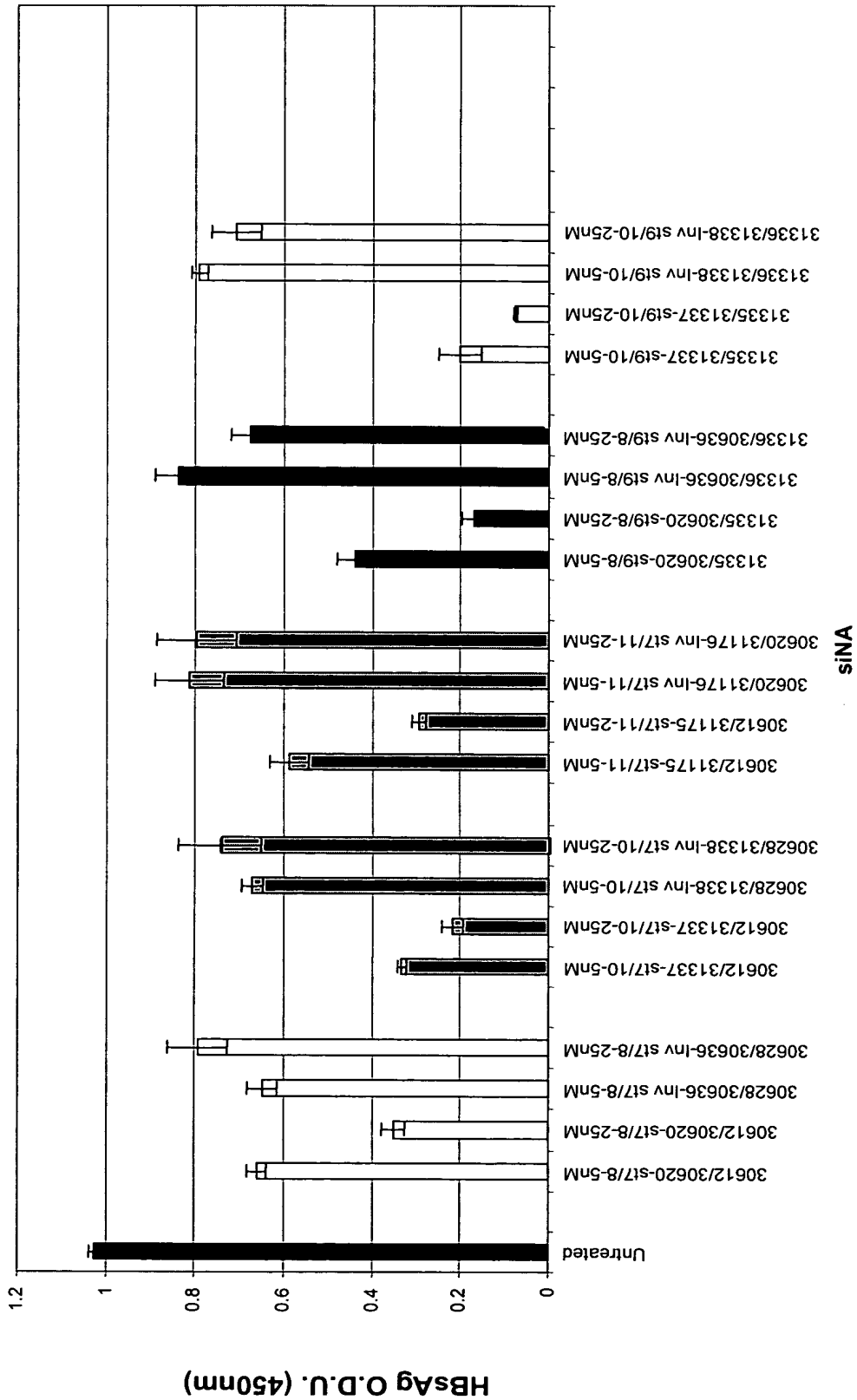


Figure 89: HBV/siNA to site 1580 Combination Constructs

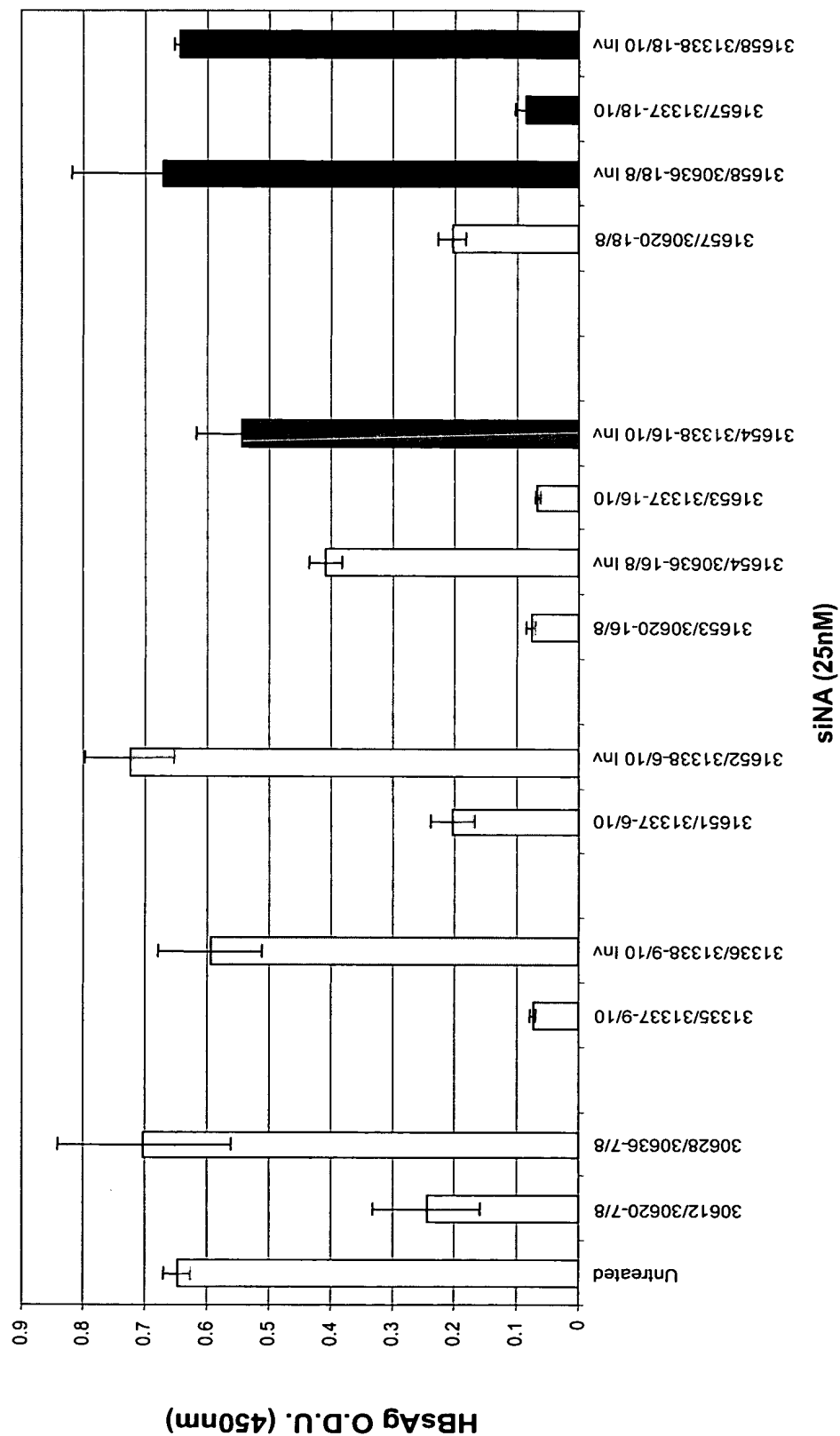


Figure 90: HBV/siNA to site 1580 Combination Constructs

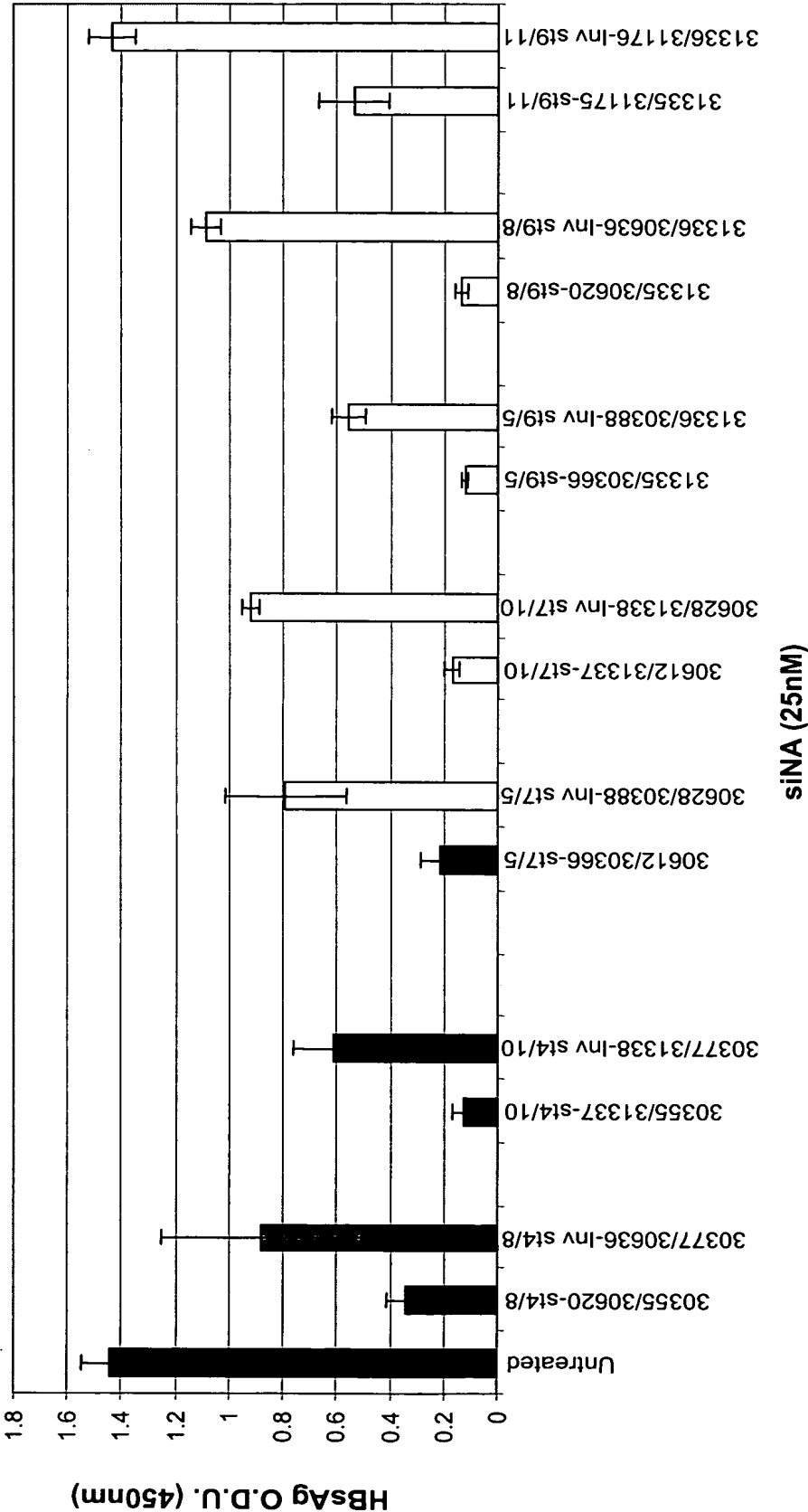


Figure 91: PEI-Peg-Gal (3:1): Demonstration of Activity & Specificity HBV DNA

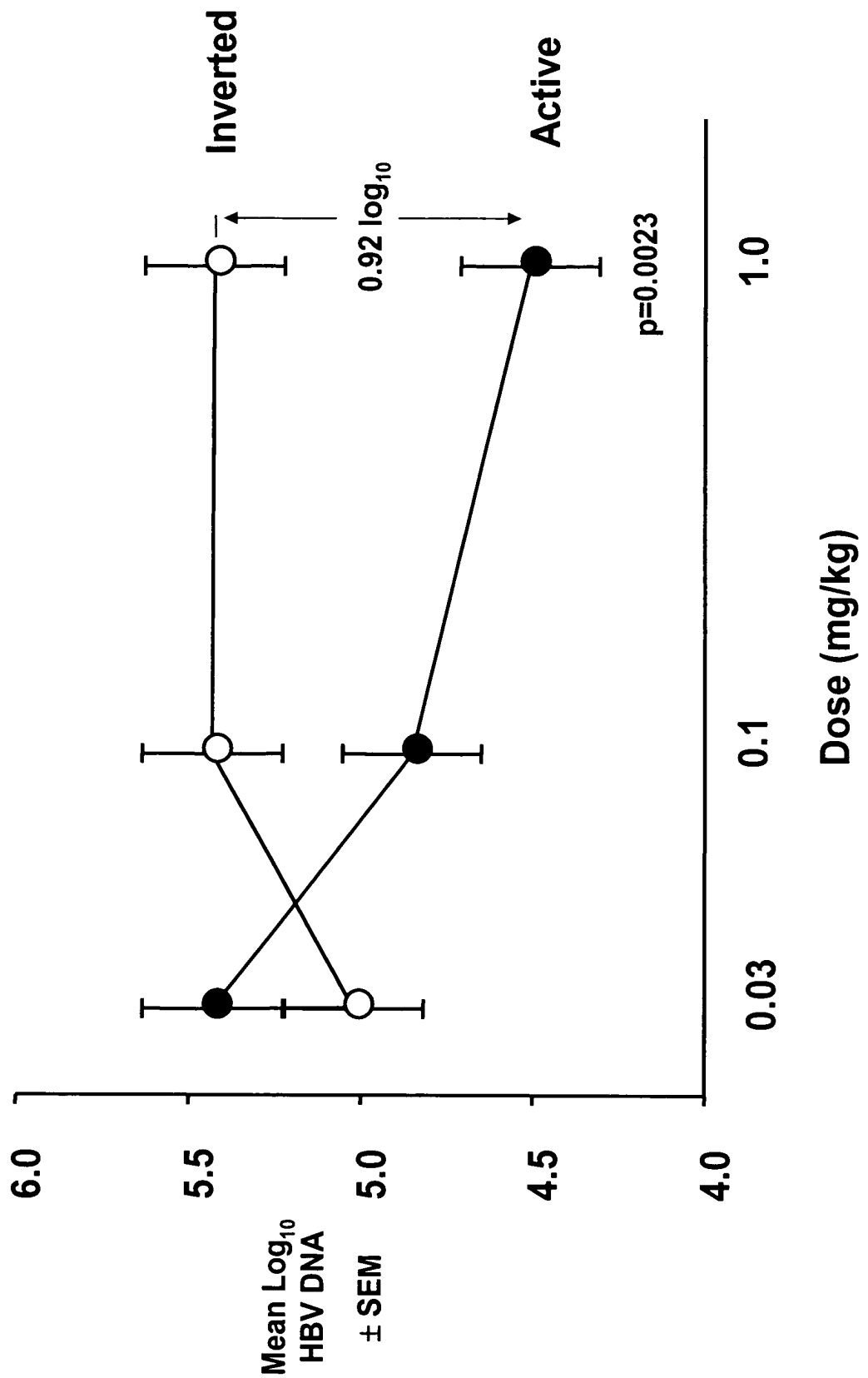
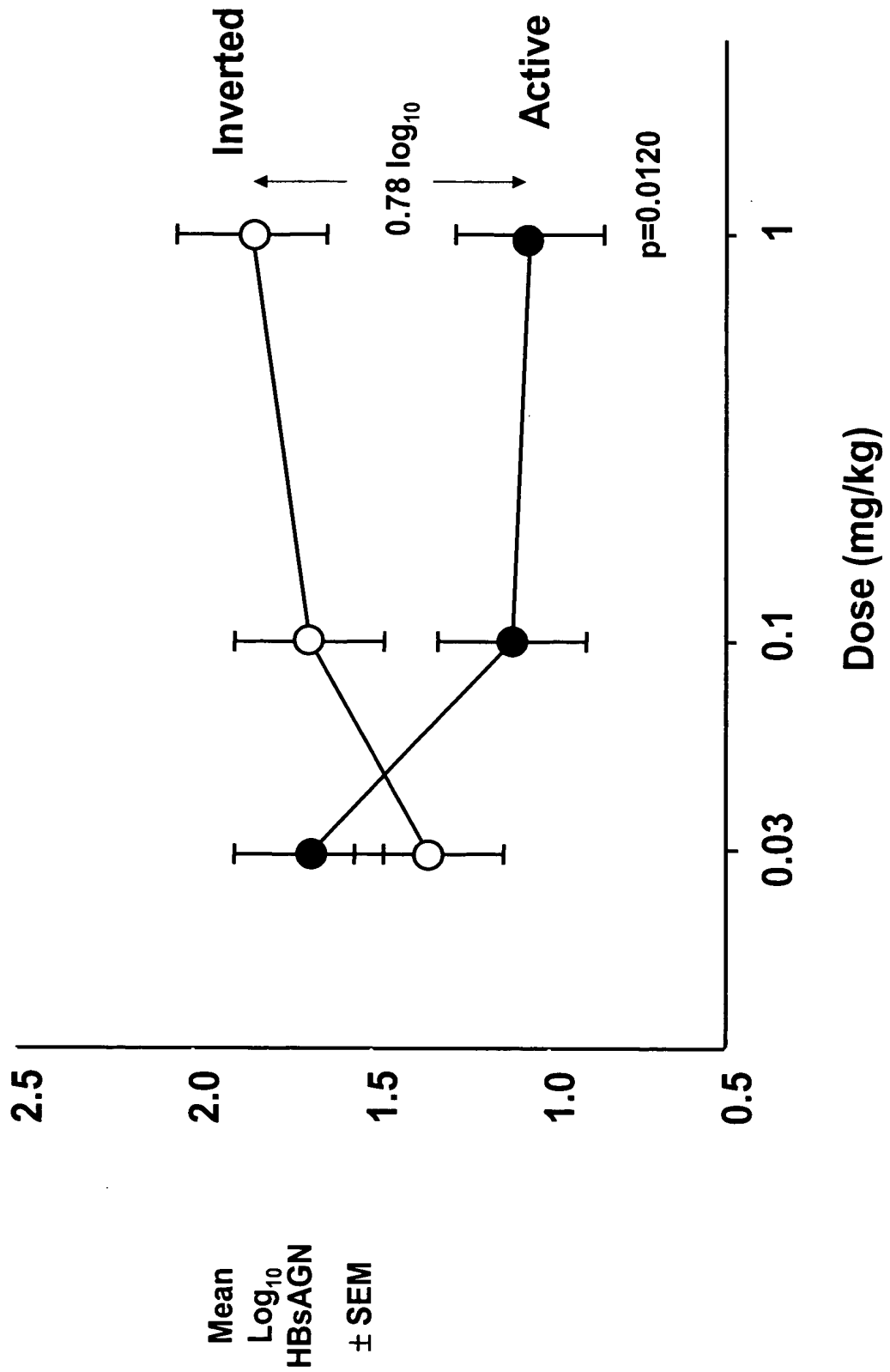


Figure 92: PEI-Peg-Gal (3:1): Demonstration of Activity & Specificity HBsAg





MW of PEI is 25000 Da

MW of PEG is 3400 Da

Figure 94A: Duplex forming oligonucleotide constructs that utilize palindrome or repeat sequences

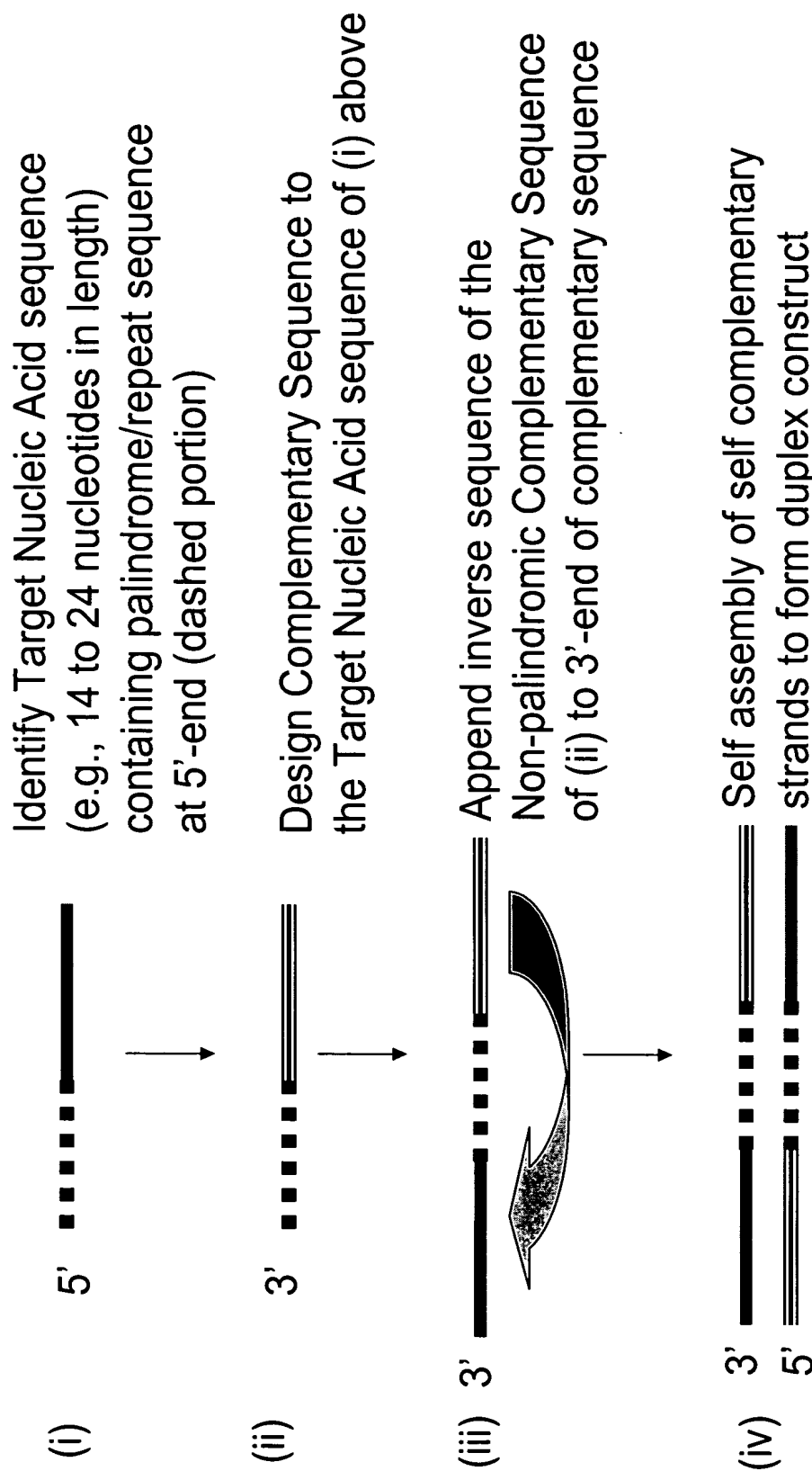


Figure 94B: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence

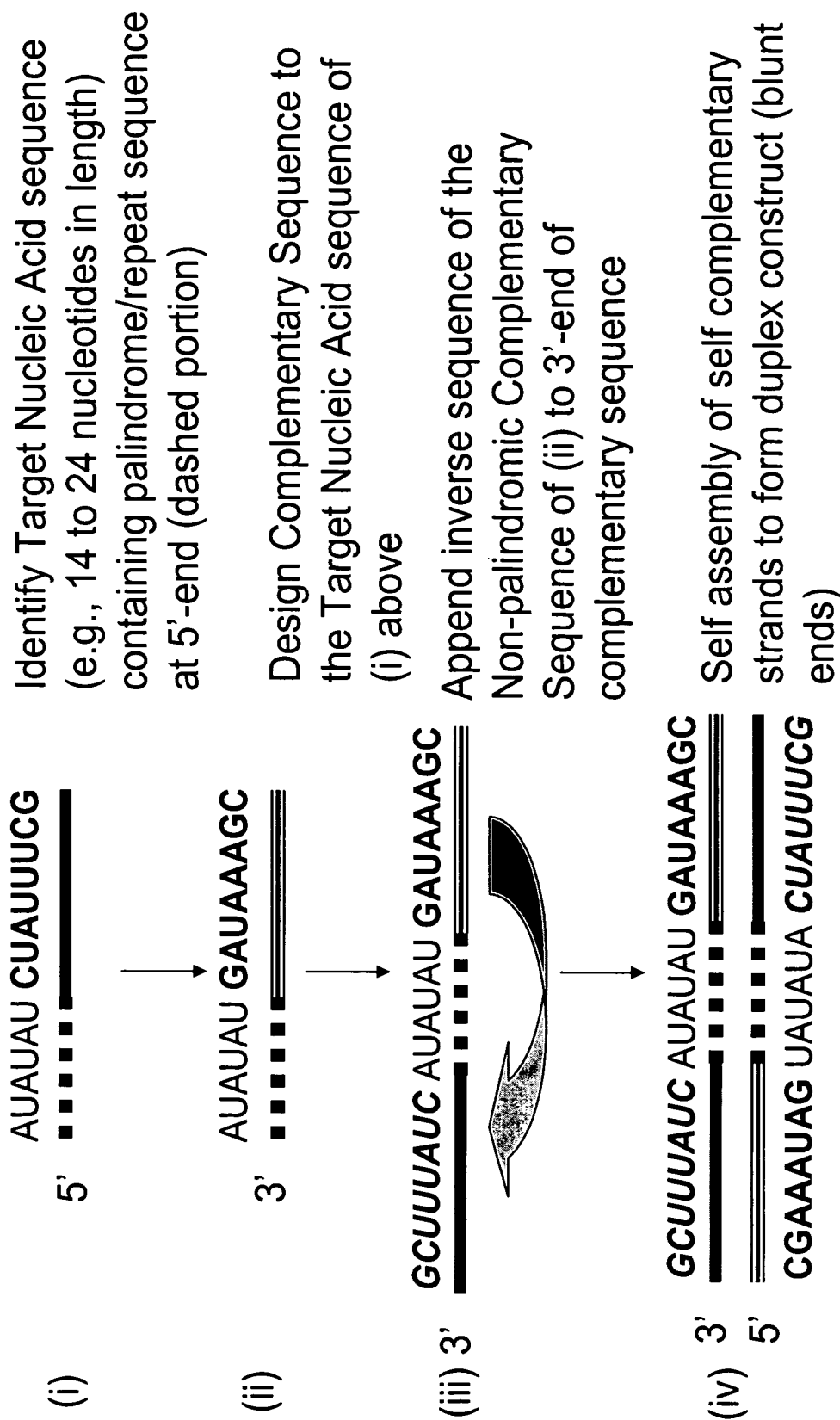


Figure 94C: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly

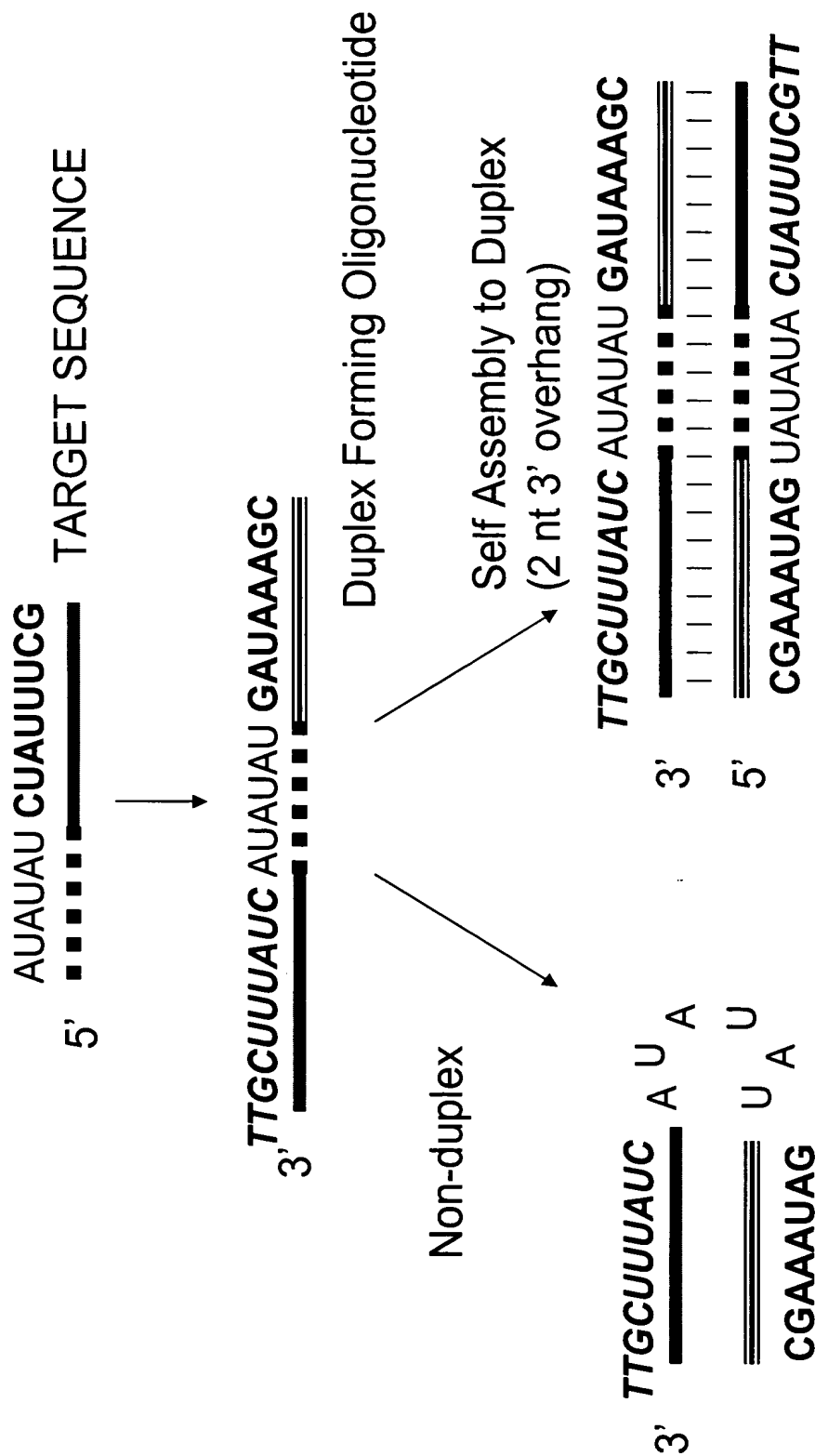


Figure 94D: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition of Target Sequence Expression

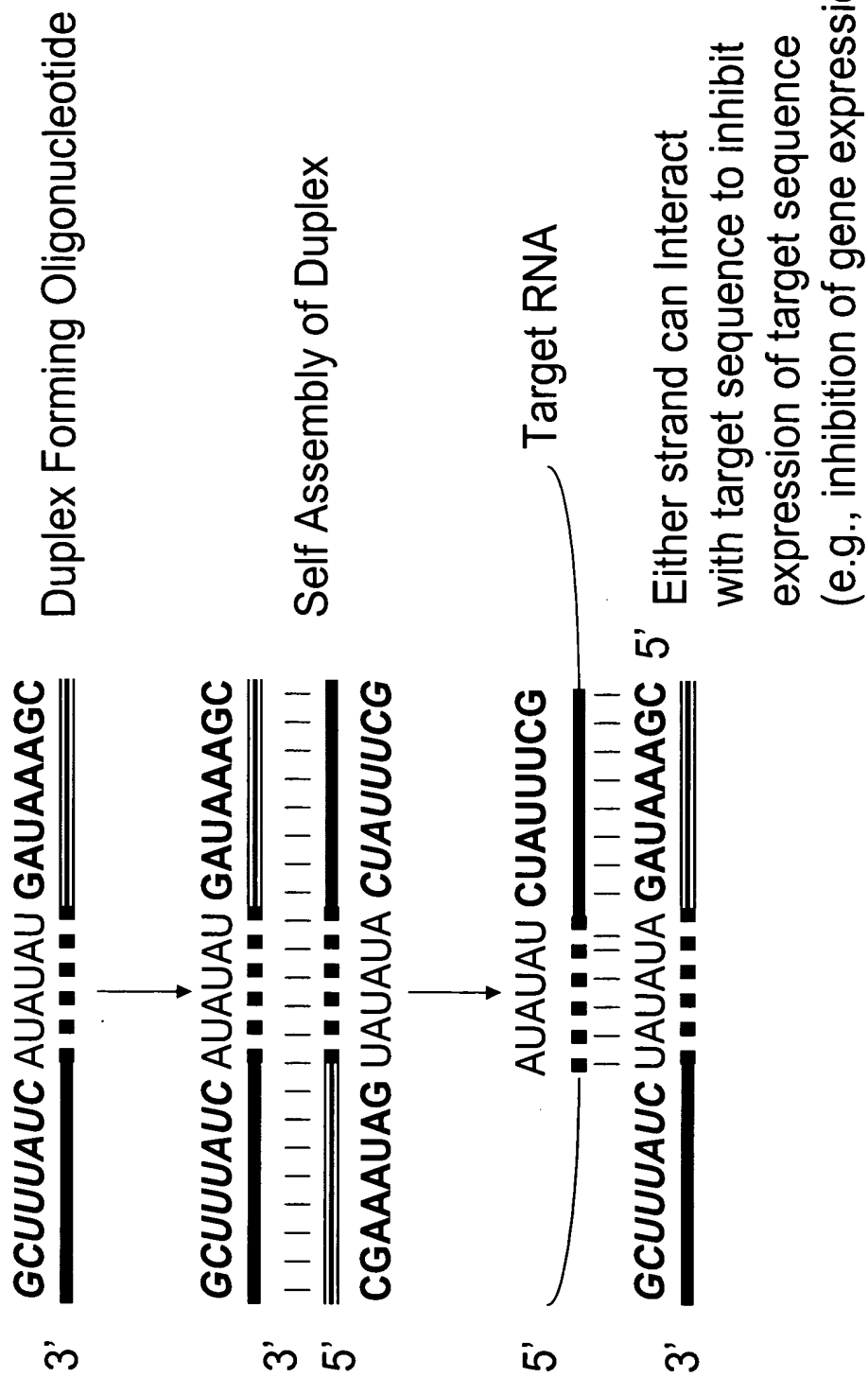


Figure 95: Duplex forming oligonucleotide constructs that utilize artificial palindrome or repeat sequences

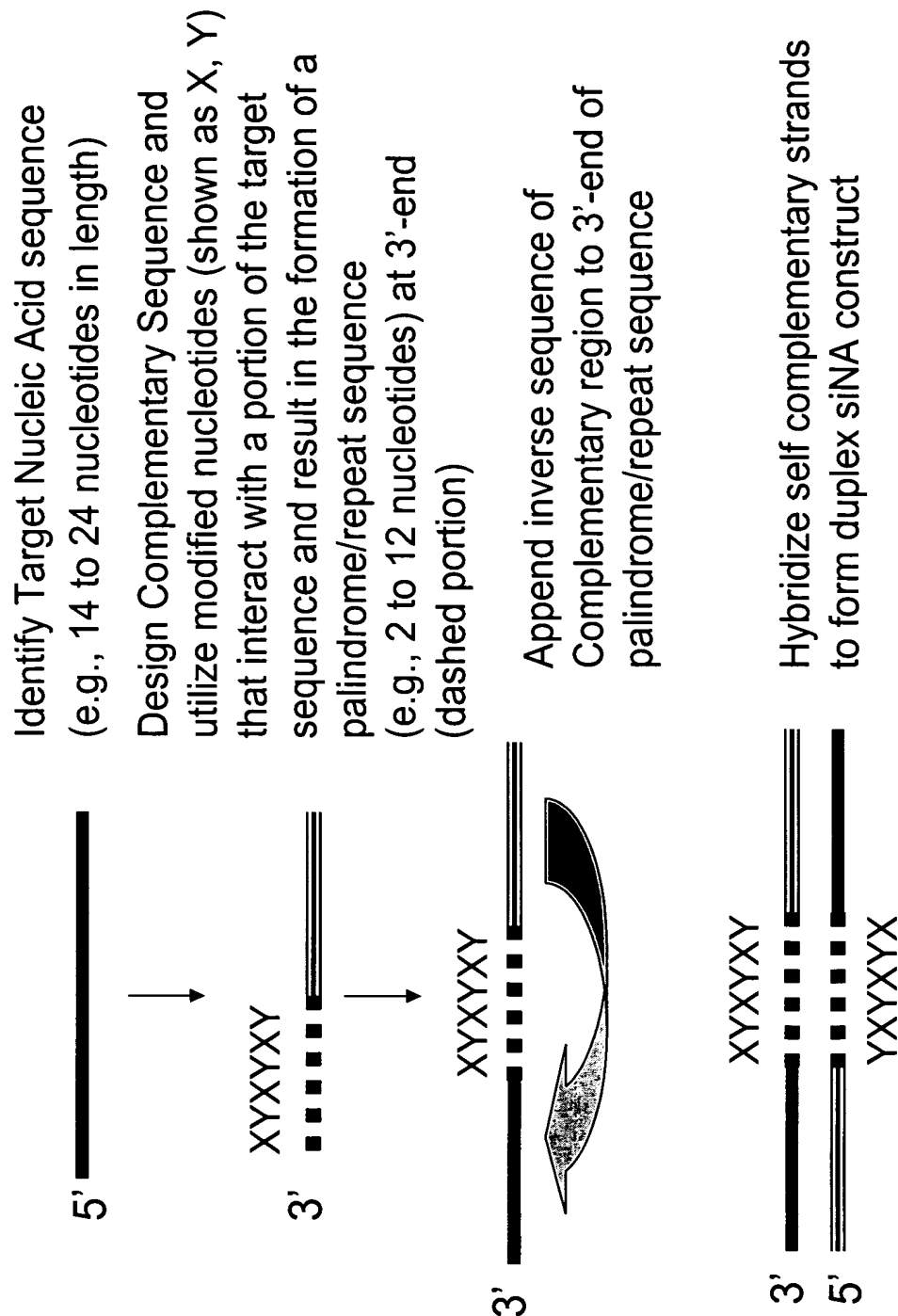


Figure 96: Examples of double stranded multifunctional siNA constructs with distinct complementary regions

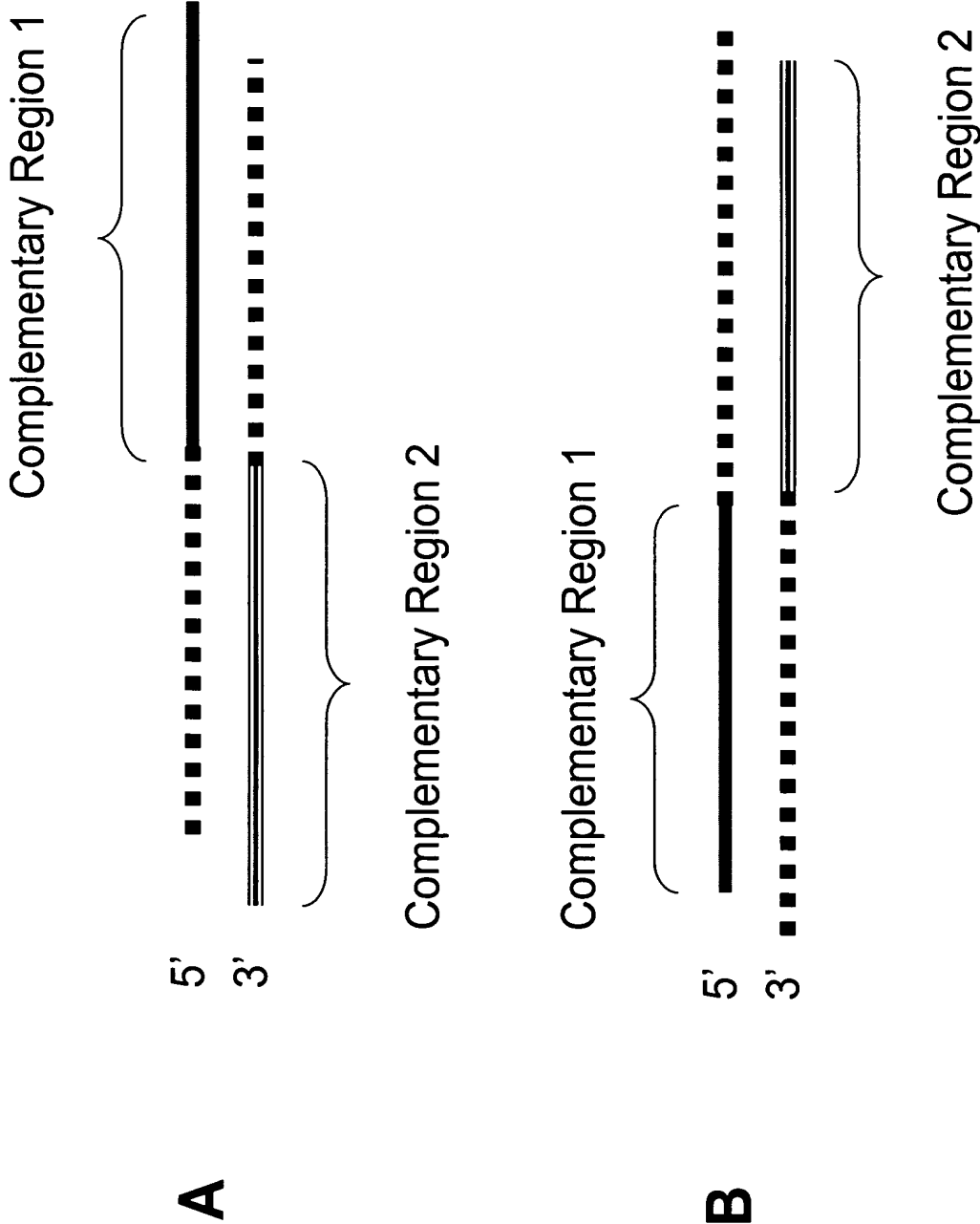


Figure 97: Examples of hairpin multifunctional siNA constructs with distinct complementary regions

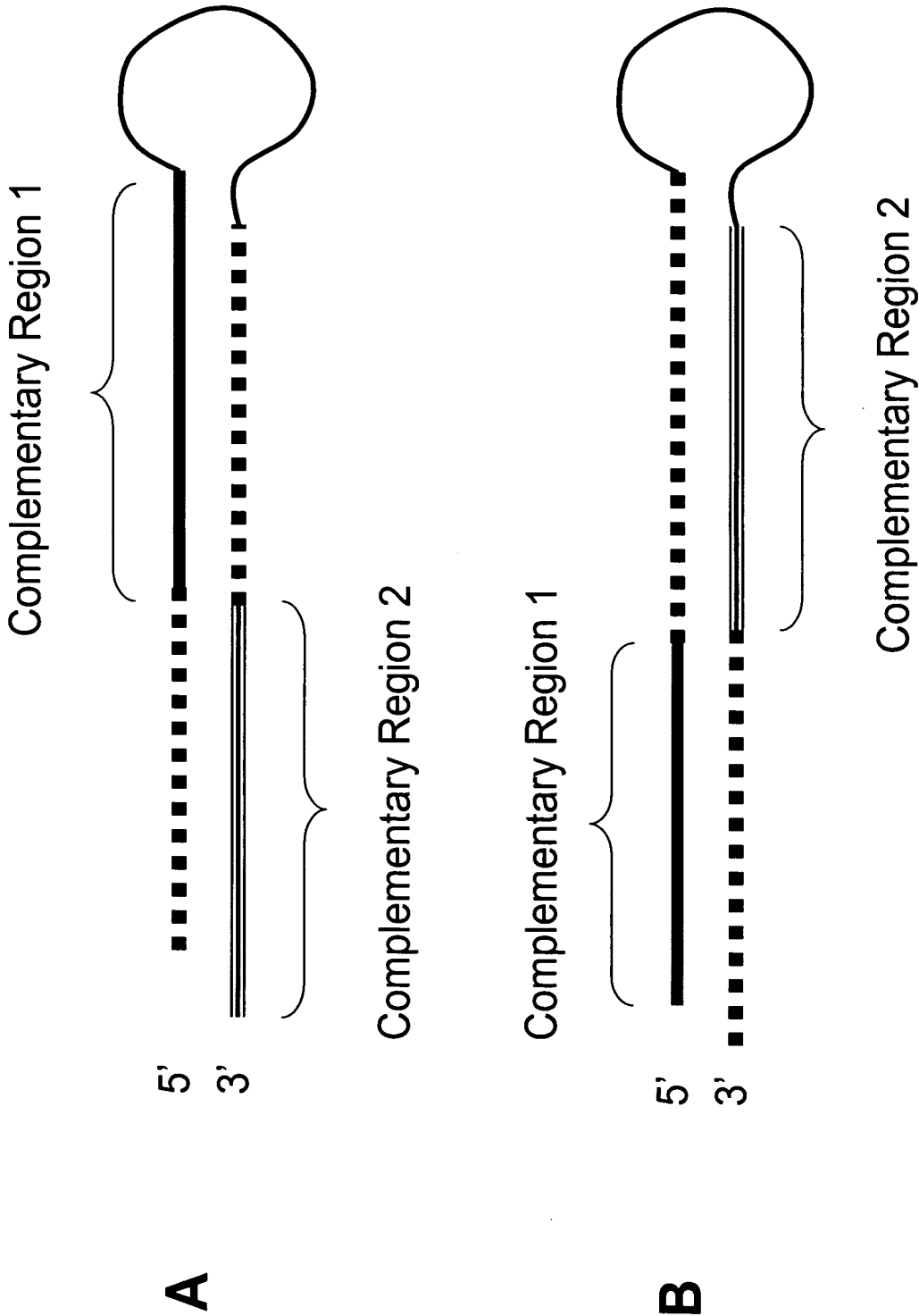


Figure 98: Examples of double stranded multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region

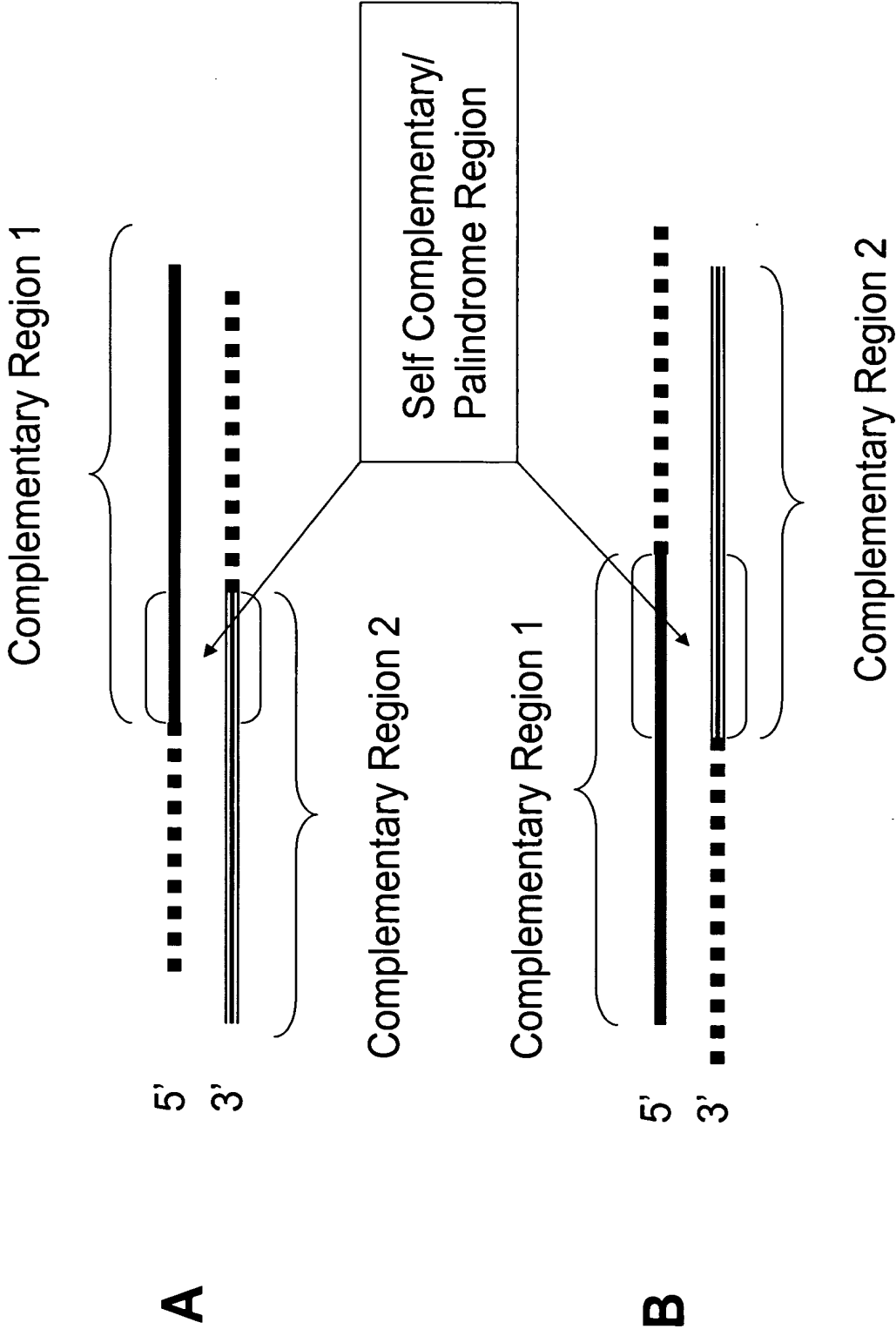
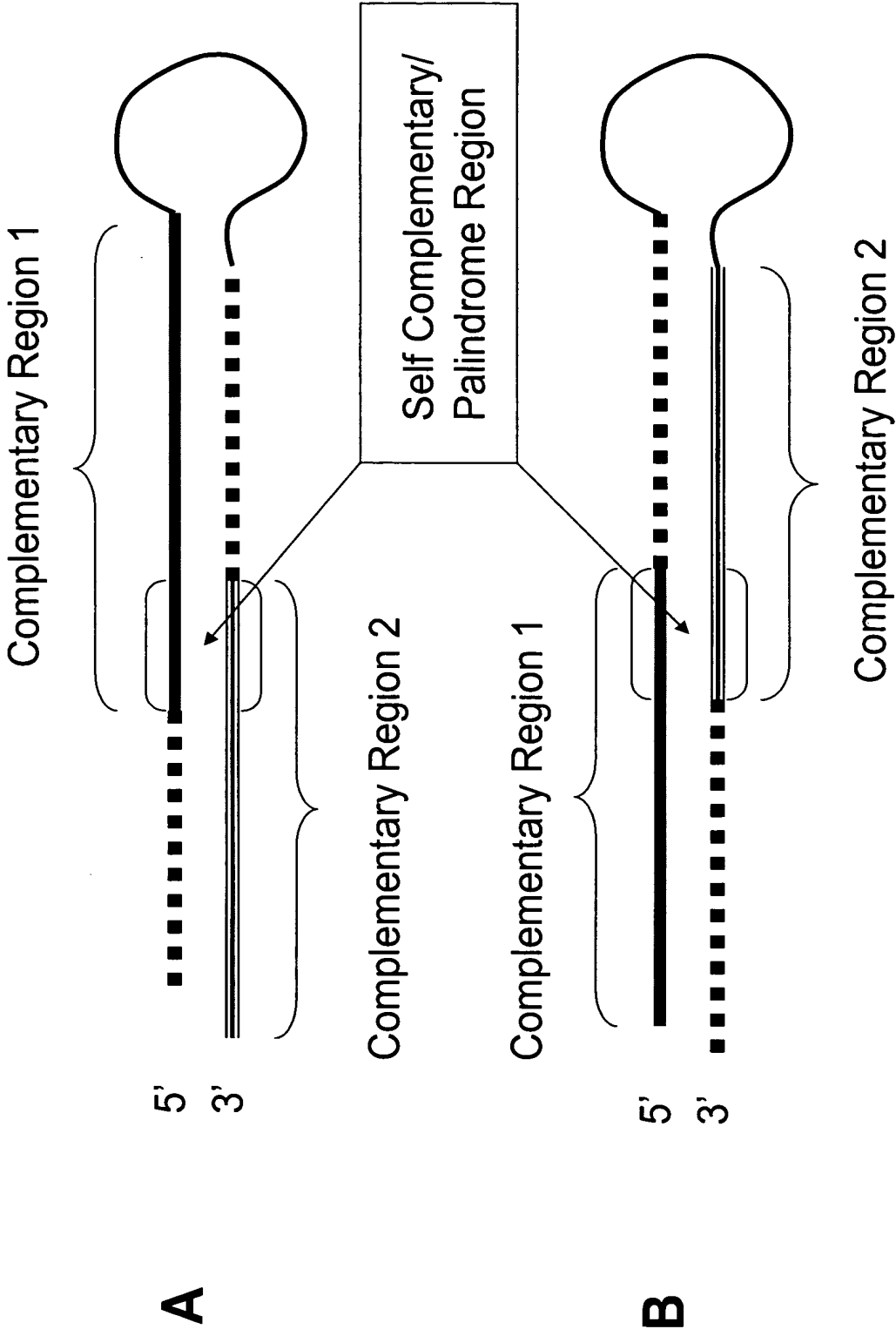


Figure 99: Examples of hairpin multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region



**Figure 100: Example of multifunctional siNA targeting two separate
Target nucleic acid sequences**

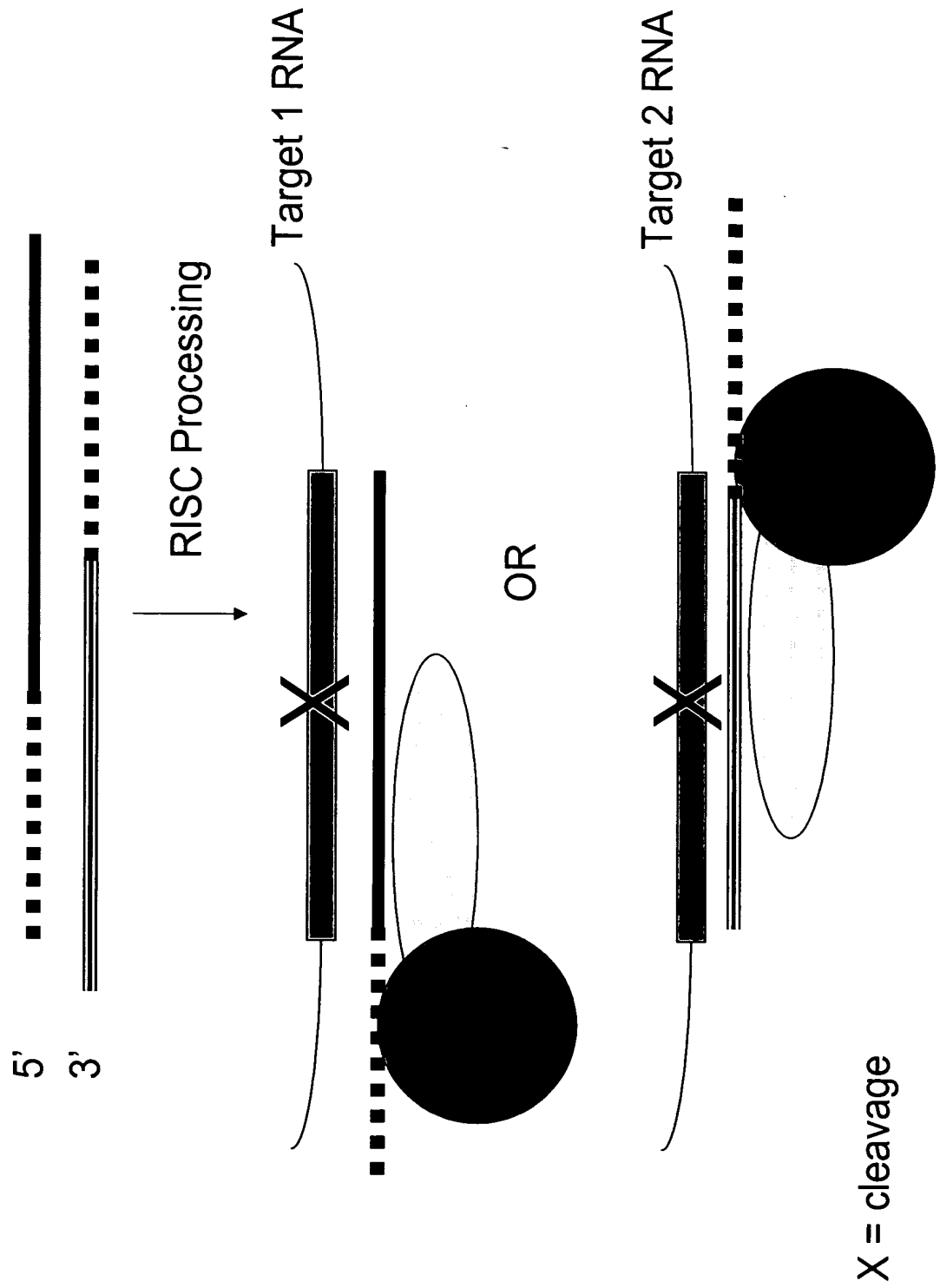
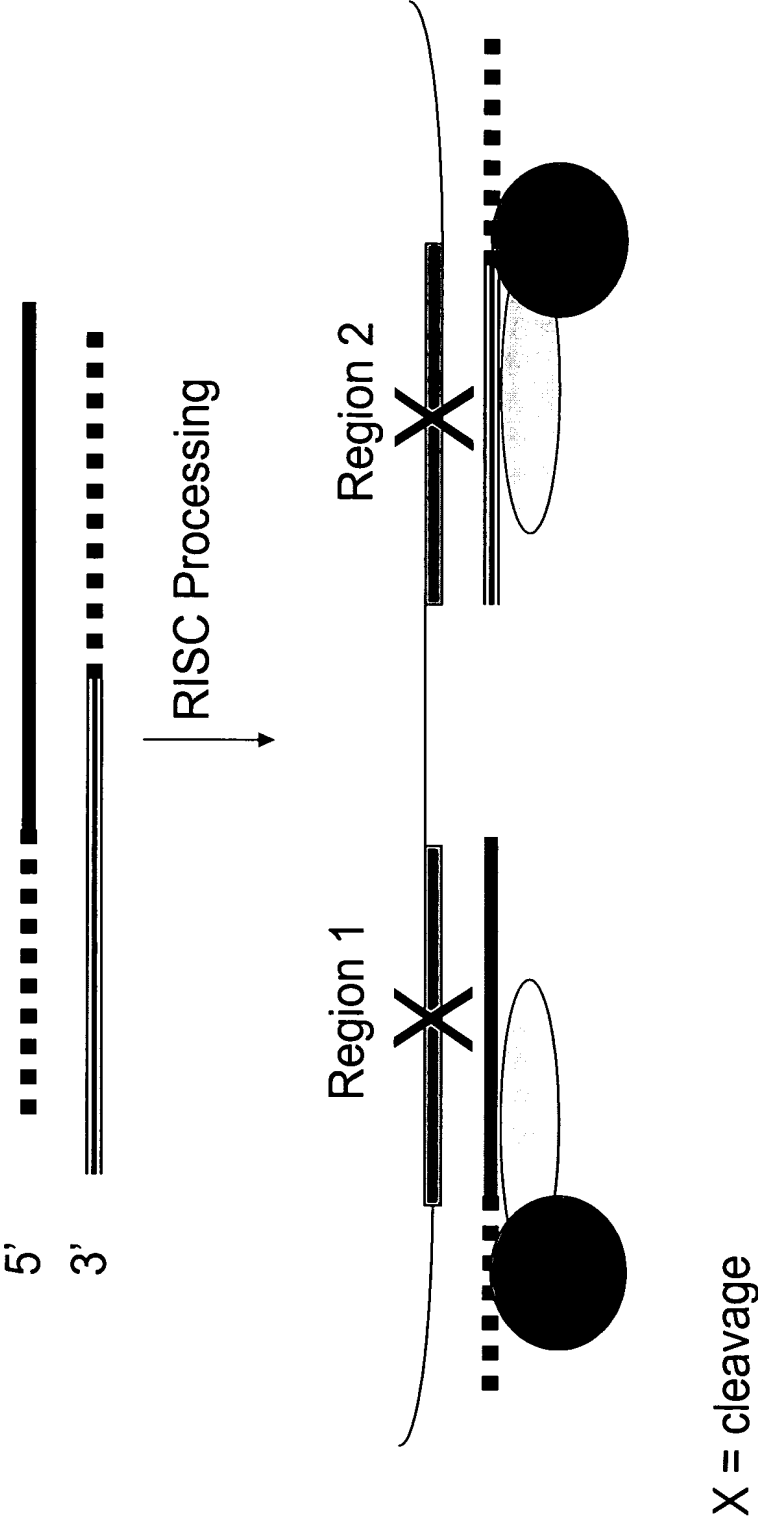
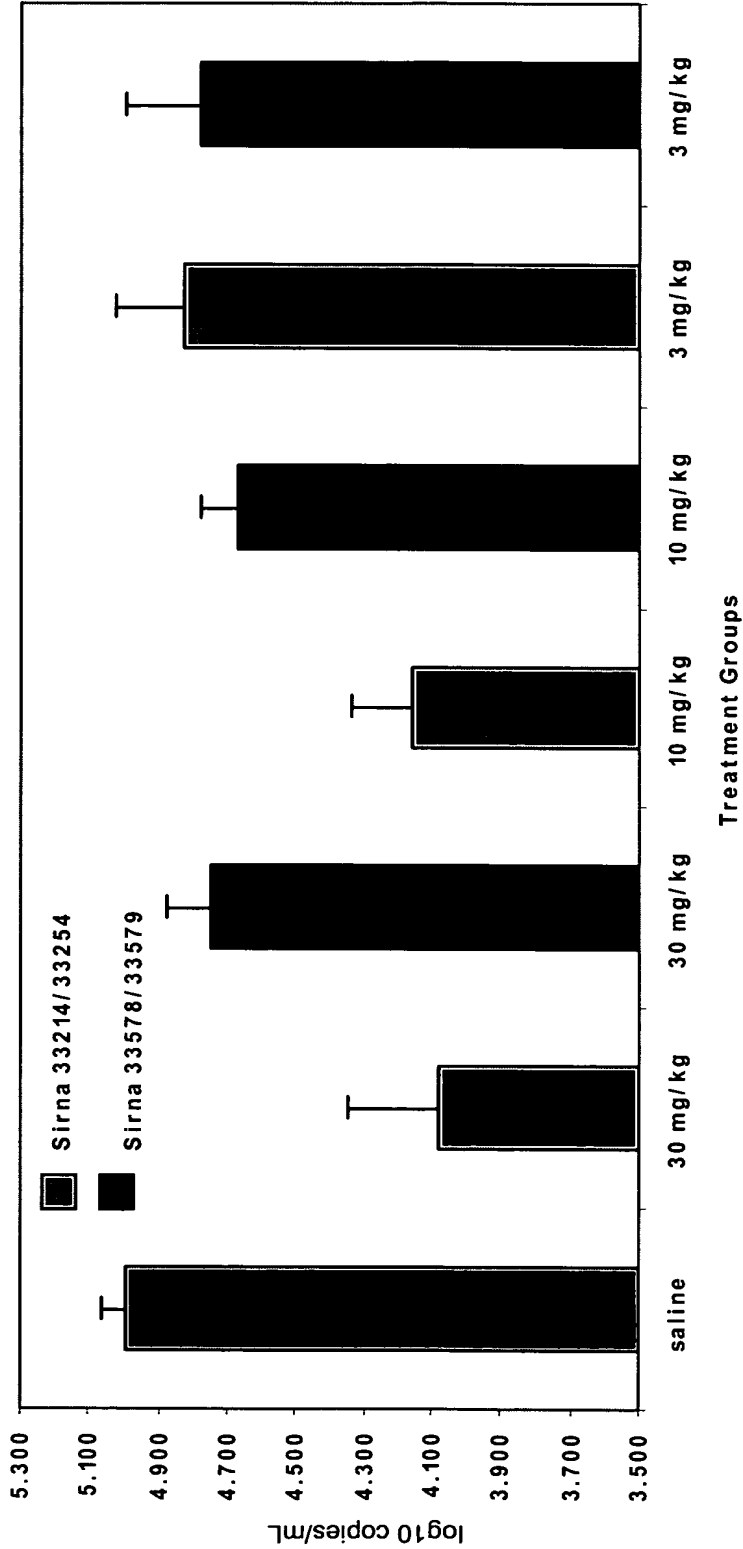


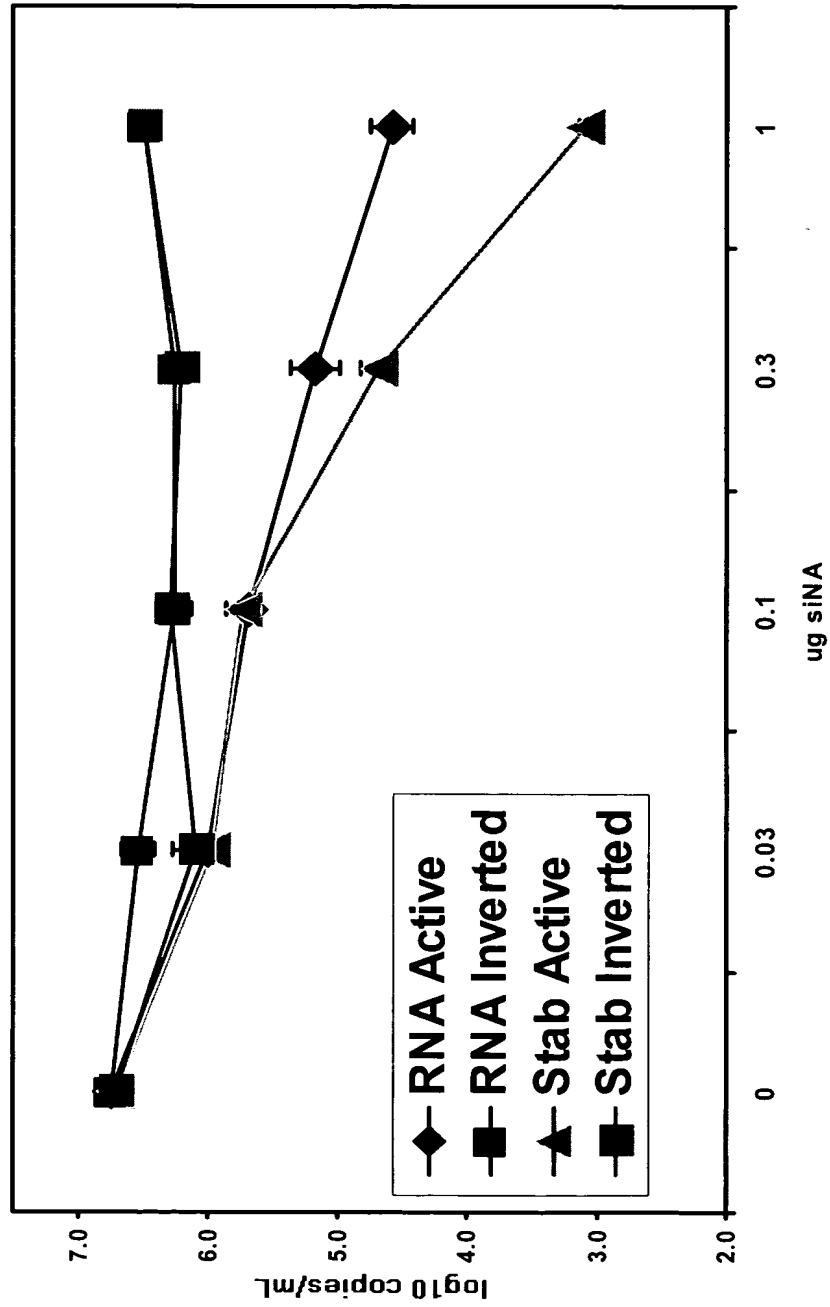
Figure 101: Example of multifunctional siNA targeting two regions within the same target nucleic acid sequence



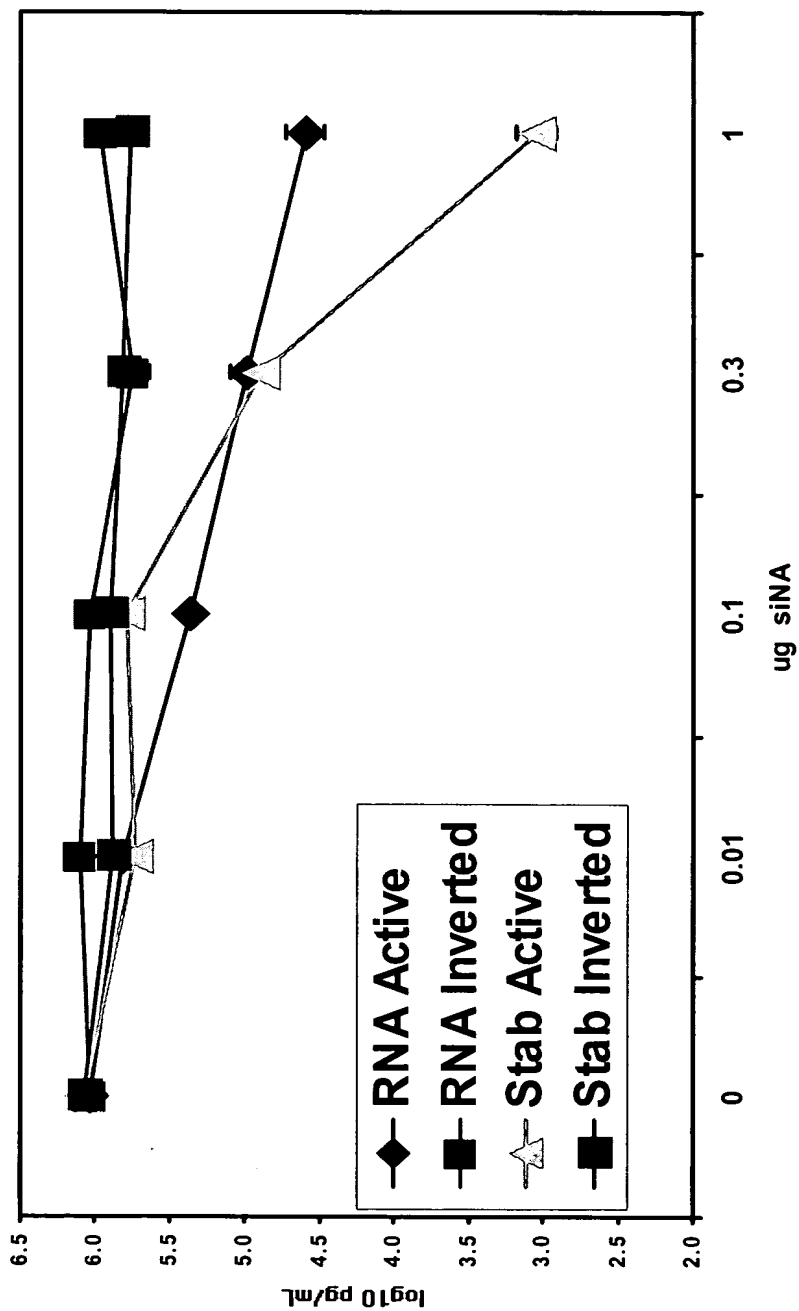
**Figure 102: Activity of Systemically Administered Stabilized
siNA in HBV Mouse Model:
Serum HBV DNA Levels**



**Figure 103A: Activity of Systemically Administered Stabilized
siNA vs all RNA siNA in HBV Mouse Model:
Serum HBV DNA Levels**



**Figure 103B: Activity of Systemically Administered Stabilized
siNA vs all RNA siNA in HBV Mouse Model:
Serum HBsAg Levels**



**Figure 103C: Activity of Systemically Administered Stabilized
siNA vs all RNA siNA in HBV Mouse Model:
Liver HBV RNA Levels**

